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DWARFISM IN BEEF CATTLE

A Literature Review

by

Carl B. Roubicek, R. T. Clark, and O. F. Pahnish

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Office of the Coordinator
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DWARFISM IN BEEF CATTLE

A preliminary review of pertinent literature compiled by research workers in the Western Region cooperating under Regional Research Project W-1.

This material has been assembled by Carl B. Roubicek, Professor of Animal Husbandry, University of Arizona; R. T. Clark, Coordinator, Beef Cattle Breeding Research, U. S. Department of Agriculture, Denver, Colorado; and O. F. Pahnish, Assistant Professor of Animal Husbandry, University of Arizona, with the assistance of Professor P. W. Gregory, University of California; Professor Ralph Bogart, Oregon State College, and Assistant Professor P. O. Stratton, University of Wyoming.

TABLE OF CONTENTS

INTRODUCTION

Recent investigations of dwarfism in beef cattle have caused many research workers a great deal of concern because of apparently conflicting experimental results. The earlier work had been chiefly concerned with inheritance of dwarfism and the identification of dwarf transmitters. However, as the work progressed, it became evident to many of these people that the positive classification of animals into dwarf and normal types was not as simple as at first assumed.

Relatively little information is available on inherited or experimental dwarfism in domestic animals. In the past, a large part of the research effort on dwarfism has been devoted to the study of the syndrome in humans. Many of the same problems that are causing confusion in the cattle research have also perplexed the investigators of human dwarfism. A literature review of dwarfism, including human dwarfism, may help to resolve some of this confusion and bring more clearly into focus experimental paths which will lead us to a quicker solution of the problem.

No claim can be made that this review is all-inclusive or complete. Actually, many articles were reviewed that did not appear to be directly related to the subject and so were not included in the list of references. Foreign articles or papers in not readily available journals were not included unless they made a noteworthy contribution.

In general, the terminology and nomenclature of the scientific papers quoted were not modified. Since many of the terms used are technical, medical descriptions, it often would have been necessary to substitute a long, descriptive phrase for a single word. Also, substitutions for the authors' terminology could lead to an interpretation different from that which was originally intended. In order to aid the reader, some of these technical words and their definitions are included in a glossary.

The general order of subject presentation is somewhat arbitrary but was intended to be in logical sequence. Duplication of material under the various headings is avoided as far as possible. Thus, the review must be considered as a whole rather than each section in itself.

The term "dwarf" is generally recognized as an individual who is conspicuously smaller than others of his kind. Many forms of dwarfism are apparent; in most instances, the relationship of these various forms is not clearly understood. It does appear that the thyroid and pituitary glands are in some way involved in most forms of dwarfism.

The thyroid is located in the neck near the junction of the larynx and trachea. Its function is the elaboration, storage and discharge of the hormone called iodothyro-globulin. Thyroxine is an effective amino acid constituent of this protein molecule (232).

Each lobule of the thyroid is composed of an aggregation of spherical or ovate cyst-like vesicles of variable size. These units are the follicles or alveoli. The interfollicular areas are occupied by loose connective tissue. Masses of epithelial cells are occasionally present between the follicles.

The follicles are lined by a secretory epithelium composed of a single layer of cuboidal or low columnar cells. The closed cavities of the follicles normally contain a homogeneous, gelatinous, amber-colored globulin. This secretion is the colloid and is a condensed storage product of the secretory epithelium.

The pituitary gland, or hypophysis cerebri, is a compound organ of internal secretion located in the sella turcica, a concavity in the sphenoid bone. The hypophysis consists of an anterior lobe, an intermediate lobe, and a posterior lobe.

The anterior lobe is composed of irregular masses and cords of epithelial cells separated by sinusoids and by a loose framework of connective tissue. Three different groups of cells are found. The chromophobes are devoid of specific cytoplasmic granules. The acidophiles have cytoplasmic granules and basophiles contain granules which have an affinity for basic dyes.

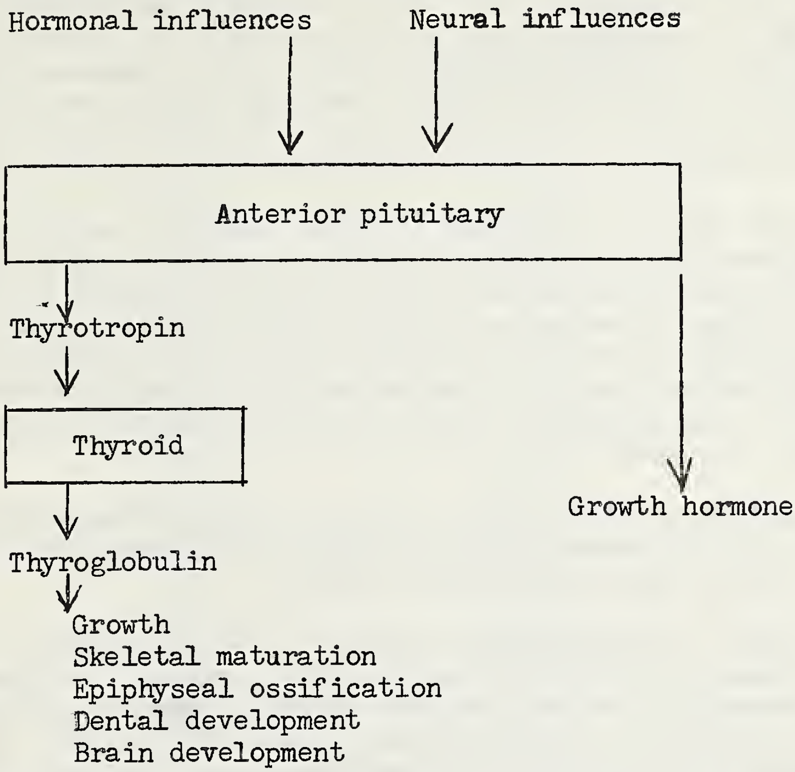
The functions of the anterior pituitary are most important in all phases of animal growth and metabolism. Some of the primary functions that have been determined are as follows:

1. Growth hormone (from acidophilic cells)
2. Sex stimulating hormone
3. Thyrotropic hormone (stimulates thyroid)
4. Adrenotropic
5. Lactogenic
6. Diabetogenic principle (causes rise in blood sugar)
7. Pancreatropic
8. Nitrogen metabolism regulating hormone
9. Fat metabolism regulating hormone
10. Parathyrotropic
11. Erythropoiesis hormone

The thyrotropic hormone secreted by the anterior pituitary gland is essential for the normal anatomy and physiology of the thyroid gland. The interrelationship between the two glands is mutual in that the secretion of the thyroid hormone likewise influences the pituitary gland, at least in respect to its thyrotropic hormone. An excess of thyroid hormone suppresses the output of thyrotropic hormone from the pituitary, thereby resulting in a diminished activity of the thyroid gland itself. The presence of circulating thyroxinedefinitely interferes with the response of the thyroid to injected thyrotropic hormones (41).

The hormone of the thyroid is commonly called "thyroxine". Thyroxine is not found as such in the thyroid but in the form of a protein, thyroglobulin. Highly purified thyroglobulin, when analyzed, yields: cystine, 41.30 percent; methionine, 1.31 percent; tryptophane, 1.88 percent; tyrosine, 3.00 percent; diiodotyrosine, 0.67 percent; thyroxine, 0.28 percent; and glucosainine, 2.20 percent (97). It has been estimated that the average person contains the equivalent of about 14 mg. of thyroxine. In the vertebrates, a delicately balanced relationship is maintained between the amounts of thyroid hormone produced and stored or released by the thyroid, and of thyrotropin produced and stored or released by the pars anterior of the pituitary. The thyroid hormone inhibits the production and release of thyrotropin and may even inhibit the making of further thyroid hormone by the thyroid gland itself (1).

Disorders of the thyroid are associated with dwarfism as well as other related effects. This can be shown diagramatically (241).



The activity of the thyroid may be altered in a number of ways (241):

1. Congenitally absent or defective, or may be injured by disease or radiation

2. Sufficient iodine may not be available to permit synthesis of an adequate supply of hormone

3. Disorders of pituitary may lead secondarily to changes in thyroid activity

4. Nervous stresses acting through the hypothalamic-pituitary pathways increase thyroid activity and are probably a factor in thyrotoxicosis

5. Alterations in the peripheral demands of the body, such as occur in pregnancy and other conditions, affect the secretory activity of the thyroid

6. Thyroid enlargements have been produced experimentally by high protein diets, excessive consumption of liver, high calcium diets, and goitrogenic substances--in general, they cause a disturbance in the metabolism of iodine

7. Thiourea and thiouracil compounds which impair the ability of the thyroid to synthesize iodothyroglobulin

8. Temperature

Hyperactivity of the thyroid, called "Graves' disease" in humans is characterized by an increased metabolic rate. Twenty-six varieties of Graves' disease have been described (23). The individual shows nervous tension, is underweight and exophthalmic. The gland itself is usually normal in size. Hyperplasia indicates hyperactivity, but not necessarily hyperfunction (146)(23). In hyperthyroidism, a very low content of thyrotropin is found in blood and urine. Lack of vitamin A leads to increased thyroid activity and increased thyrotropic potency of the pituitary gland (1).

The hyperactive thyroid may change to hypo- type very rapidly. The thyroid becomes exhausted and the hormone becomes of poor quality and quantity. A very marked seasonal variation exists in the percentage of iodine present in the healthy, normal-sized thyroid glands of sheep, beef, and hog. There is in general about three times as much iodine present in the glands in the months between June and November as in the months between December and May (202). The glands are larger during the months in which the lower iodine content was observed.

The iodine content in milligrams per gram of dried gland has been determined to be 3.46 for normal glands, 1.65 for early hyperplastic glands, and 0.19 for the markedly hyperplastic gland.

In pregnant cows, the thyrotropic content of the pituitaries is greater in early pregnancy and falls during the late pregnancy to approximately the amount present in the non-pregnant animals. There is less thyrotropin in the pituitaries of dry, pregnant animals than in dry, open ones; but more thyrotropin in lactating, pregnant ones. Likewise, the hormone is more abundant in lactating, pregnant cows than in dry, pregnant animals. The thyrotropin content of dairy cow pituitaries is consistently greater than in beef cow pituitaries (1).

The thyroid and parathyroid glands function very early in embryonic development. The thyrotropic action of the hypophysis is also manifest very early. Apparently, the characteristic relationships between hypophysis and thyroid establishes itself simultaneously with histological differentiation of the glands (70). The function of the endocrine glands during fetal life is insignificant under optimal environmental conditions of fetal development. As soon as deviation from the optimum occurs, the endocrine system can be mobilized as one of the most important regulators of vital functions in the organism (225).

The fetal thyroid tissue possesses a strong selective affinity for iodine. The glands of beef fetuses contain an appreciable amount of iodine as early as the third month of intra-uterine life. The iodine content increases proportionately with the age of the fetus. Glands from 705 beef fetuses from 6 to 9 months of age were analyzed and the following observations made (72):

1. Individual fetal thyroids vary enormously in size and color.

2. The average weight of normal fetal glands is 9.6 grams with a maximum of 19.8 grams and a minimum of 1.7 grams. The average weight of large fetal glands is 40.0 grams, maximum of 194.0 grams and a minimum of 20.2 grams. The average weight of adult thyroids is 36.2 grams.

TABLE 1.--Percentage of iodine and moisture in dried beef thyroid glands collected bi-weekly for one year (202).

Date	% Iodine	% Moisture Lost at 97.5	% Iodine Calculated to Dry Basis
Jan. 7	0.101	7.69	0.109
Jan. 21	0.045	9.44	0.050
Feb. 4	0.026	8.41	0.028
Feb. 18	0.107	0.80	0.108
Mar. 3	0.053	7.63	0.058
Mar. 17	0.038	3.88	0.040
Mar. 31	0.059	1.38	0.060
Apr. 14	0.068	9.71	0.075
Apr. 28	0.069	3.14	0.071
May 12	0.072	9.33	0.079
May 26	0.095	10.42	0.106
June 9	0.130	10.58	0.145
June 23	0.170	11.17	0.192
July 7	0.288	13.38	0.332
July 21	0.298	11.12	0.335
Aug. 4	0.267	13.48	0.308
Aug. 18	0.310	10.61	0.347
Sept. 1	0.277	3.16	0.286
Sept. 16	0.307	2.05	0.314
Oct. 1	0.240	0.66	0.242
Oct. 14	0.327	2.34	0.335
Oct. 28	0.303	1.40	0.308
Nov. 11	0.332	8.15	0.361
Nov. 25	0.225	7.24	0.243
Dec. 10	0.200	7.80	0.217
Dec. 24	0.123	6.15	0.131

TABLE 2.--Thyrotropic potency (guinea pig) units per grain of fresh anterior lobe pituitary of cattle (1).

Pre-puberty - 26.4
Puberty (4-10 months) - males, 38.36 - females, 32.13
Early sexual maturity (11-23 months) - males, 35.02 - females, 24.59
Late sexual maturity (over 2 years) - 22.53

These investigators never found a thyroid gland that did not contain iodine.

3. Normal fetal glands are relatively larger and contain more iodine and phosphorus per unit of body weight than thyroids from mature animals. The male fetal glands average 9.9 grams, female glands 9.3 grams. The female glands contain a higher percentage of iodine than the male glands. Apparently, the female metabolism requires more thyroid activity according to body weight than the male during the fetal stage as well as after birth.

4. Many fetuses show abnormally large glands that coincide in iodine and phosphorus content with goitrous glands from mature animals. This may be explained by concluding that the demand for iodine in the rapid fetal metabolism and growth, in certain instances, may exceed the available supply furnished by the pregnant animal. This supply may be sufficient for the maintenance of the maternal metabolism, leaving the adult thyroid normal, but not sufficient to prevent iodine starvation and enlargement of the fetal gland.

5. The enlarged glands contain less total iodine and much more total phosphorus than normal thyroids. This is true in both fetal and adult glands.

6. It has been demonstrated conclusively that functional therapeutic activity and presence of iodine coincide in the fetal thyroid during intra-uterine life in analogy with the conditions during extra-uterine life.

7. The iodine content of the normal-sized fetal thyroid glands during the last three months of intra-uterine life seems to be fairly uniform throughout the various seasons.

8. Normal fetal glands are relatively larger and contain more iodine and phosphorus per unit of body weight than thyroids from fully mature animals.

9. The normal female fetal thyroid glands show a higher content of iodine and seem, therefore, to possess greater functional activity than the male fetal glands.

10. Fetuses possessing enlarged thyroid glands on the whole were considerably smaller than the average fetuses of the same age with normal thyroids.

11. The enlargement of fetal thyroids exceeds both in frequency and size the number of goitrous glands of fully mature animals and is apparently the consequence of insufficient supply or faulty assimilation of iodine on the part of the pregnant animal.

12. Enlarged glands in general, both fetal and adult, contain less total iodine and much more total phosphorus than normal thyroids.

The thyroid is more concerned with the process of embryonal unfolding than with growth (205).

The attachment of the bovine embryo to the walls of the uterus by means of the union of the fetal and maternal cotyledons is a gradual process beginning about the thirty-sixth day of pregnancy in the area closest to the embryo and gradually spreading throughout the pregnant horn, the body of the uterus, and a large part of the non-pregnant horn (73). Measurements and weights of the bovine fetus show that tables for normal prenatal development can probably be established (173). Some of these data are summarized in Table 3 and Table 4 to show the developmental pattern (73, 173, 227, 245).

TABLE 3.--Embryonic age, weight and measurements from twenty-five to forty-three days:

Embryo Age (days)	Weight (gm)	Crown-rump Length (cm)	Contour Length (cm)
25 - 28	0.052	0.725	1.711
35 - 40	0.875	2.025	4.188
42 - 43	2.298	2.977	6.290

TABLE 4.--Measurements of bovine fetuses by age.

Age of Fetus (Days)	Weight (Gm)	Forehead-Rump Length (Cm)	Head Length (Cm)	Head Breadth (Cm)	Forearm Length (Cm)
45	2.77	3.08	.50	.825	.475
50	4.94	3.85	.60	.850	.500
60	13.78	6.60	1.15	1.450	1.150
70	37.25	9.40	3.30	2.000	1.900
90	159.80	16.40	5.00	3.300	2.700
100	317.20	18.80	6.00	3.900	3.300
120	820.00	27.10	8.40	5.000	5.000
140	1807.00	32.60	11.00	6.100	7.200
160	3562.00	43.70	13.20	7.500	9.100
185	6685.00	54.00	16.60	8.300	13.200
200	10433.00	58.50	18.20	9.400	18.500
230	18144.00	73.00	18.50	10.200	20.000
260	31298.00	87.00	23.00	11.500	23.000

TABLE 5.--Analysis of fetal beef thyroids (70).

	Fetus - 3 mos. old	Fetus 7-8 mos. old
Average weight per gland (gms.)	1.6	9.0
Moisture (percent)	84.1	82.3
Desiccated, fat-free gland (percent)	14.8	16.5
Iodine in fat-free gland (percent)	0.08	0.19

In the bovine, the hypophysis at birth is about .45 gram for females and .5 gram for males, although the range is from .3 to .7 gram for females and .4 to .8 for males (78).

DWARF DESCRIPTIONS - HUMAN

Dwarfism in humans has been studied rather intensively for a number of years. Much of this material has been assembled and various phases of the work are available in technical books (82, 109, 155, 175, 191, 229, 241). Background for the understanding of dwarfism in humans has been prepared in a semi-outline form (242).

Somatic growth is influenced by at least three types of hormones:

a. Pituitary growth hormone
b. Thyroid hormone
c. Androgen

All three of these have been shown to stimulate protein anabolism and increase nitrogen retention. Much remains to be learned about the details of their action, both in accelerating growth and in bringing it to an end through fusion of epiphyses. It is probable that each of these hormones manifests its effect at a somewhat different period of life and in a different way. Thyroid manifests its most important effect during the early years of life, although deficiency causes a cessation of growth at any period of childhood (242).

The period of life during which the pituitary growth hormone is elaborated and effective is not known. Some believe that it may be of relatively little importance during the first few years.

Causes of Dwarfism

I. Bone diseases:
   A. Chondrodystrophy - various types
   B. Rickets, all types
   C. Osteogenesis imperfecta
   D. Disease of the spine

II. Nutritional or metabolic disorders:
   A. Celiac disease and cystic fibrosis of the pancreas
   B. Chronic renal disease
   C. Hepatic insufficiency
   D. Hurler's syndrome of gargoylism
   E. Nutritional defects and chronic infections

III. Circulating disorders, with anoxemia:
- A. Congenital malformations of the heart
- B. Extensive chronic pulmonary disease

IV. Endocrine disturbances:
- A. Hypothyroidism
- B. Sexual precocity with early epiphyseal union
- C. Hypopituitarism
- D. Mixed types

V. Delayed adolescence with retarded growth spurt:

VI. Primordial or genetic dwarfism:
- A. Familial
- B. Sporadic
- C. Syndrome of ovarian agenesis and dwarfism

VII. Progenic types of dwarfism:
- A. Hutchinson - Gilford type
- B. Cockayne - Neill type

Cretinism:

Among endocrine disorders causing dwarfism, hypothyroidism is probably the most common (242). The incidence of cretinism, together with various types of goiter disturbance, has caused considerable confusion. Cretinism occurring in goiter areas has been designated as endemic cretinism. When cretinism occurs in regions where goiter is not endemic, it is known as sporadic cretinism. It is usually accompanied by no evidence of goiter (166).

The term "cretinism" was first used to designate endemic, congenital hypothyroidism, a disorder primarily due to iodine deficiency in the mother. In recent years, it has been used indiscriminately to refer to thyroid hypofunction in infants and young children, irrespective of the etiological cause (170).

When severe thyroid deficiency has existed over a considerable span of time during the early years of growth, it gives rise to the classical clinical picture described as cretinism. Many cretins, however, when seen during the first year or two of life, are less grotesquely abnormal, and on superficial inspection might be mistaken for fairly normal infants considerably younger than their actual age (240).

The symptomatology, physical changes and radiologic abnormalities depend upon the degree of thyroid deficiency and upon the age of the child when the disturbance commenced (82).

Hypothyroidism may exist in utero or may develop in infancy, in childhood, or in adult life. Since the thyroid hormone plays a role in growth and maturation, the effect of a lack of it during the growth period will be different and more devastating than during a time of life when full maturity and growth have been attained (155).

A child may be born normal and function normally until he is attacked by some acute infectious disease or some other acute pathological condition which produces acute thyroiditis and subsequent atrophy of the thyroid gland. It seems in these cases that during this acute attack there is a call for thyroid on the part of the body. It is supplied at the expense of a diminished reserve (83).

Cretinism is seldom recognized at birth. Retardation of physical and mental development becomes more noticeable in the following months, and by the end of the first year the clinical picture has often developed (112, 172).

If thyroid deficiency does not occur until in later childhood, the patient will have attained such growth that he cannot be classified as a dwarf (74, 240).

The relation of thyroid insufficiency in the mother probably bears a definite relationship to the occurrence of the myxedema and cretinism in her children. Furthermore, it is probable that the time of incidence of the greatest thyroid deficiency of the mother during her pregnancy has a bearing upon the development of the brain of the fetus. Another factor is insufficient maternal thyroid during the period of lactation. It would appear that the possibilities are these:

a. Insufficient maternal thyroid secretion during pregnancy with consequent neural defects in the offspring

b. Insufficient thyroid in the newborn, uncompensated, due to insufficient thyroid in the maternal or other milk

c. Insufficient thyroid in the newborn, compensated for by the maternal milk, such cases becoming hypothyroid after lactation is over

Pregnancy is said to protect some females from incipient myxedema, the disease establishing itself only after parturition or at the approach of menopause, but in other cases pregnancy appears to aggravate the disorder (191). It has been estimated that 82-85 percent of people affected with thyroid disease are females. It seems possible that this is due to the alterations in metabolism incident to pregnancy (129).

Although cretin symptoms may not be marked during the first year and a half of life, it appears that even then the patients had a congenital deficiency. Some thyroid function was present that later was lost.

The differentiation of complete cretinism, partial cretinism, infantile myxedema and juvenile myxedema is hard to make because hypothyroidism has a gradual and insidious onset, because maternal hormone, absorbed by the child in utero, affords protection from symptoms for a considerable time, and because minor amounts of hormone may be obtained from milk and food (81).

When an individual affected with thyroid disturbance becomes pregnant, unless that disturbance is counterbalanced by exceptionally favorable conditions, there will be a more or less severe form of fetal athyreosis and grave disturbances will be produced in the maternal organism also (83). Female animals have more iodine per unit of body weight than

males. They are, hence, more susceptible to iodine shortage. Temporary physiological enlargement of the gland may take place in females at puberty or perhaps in cold weather (74).

Pathologically, three types of thyroid deficiency in children can be recognized (175):

a. Absence of the gland
b. Atrophy of the gland
c. Enlargement of the gland

Absence of the gland:

Athyreosis may result from failure of the gland to develop during embryonic life or from wasting of the gland at some time during or shortly after intra-uterial life.

Atrophy of the thyroid gland: (Incomplete)

Atrophy of the thyroid gland may occur either spontaneously shortly before or after birth, or following a childhood intoxication or infection in a previously normal child.

Enlargement of the thyroid gland:

Pathologic processes may be present at birth but the clinical picture is not fully developed until some time later. This is referred to as "sporadic cretinism."

If thyroid function ceases in a previously normal (enthyroid) child before full stature and maturity are attained, the manifestations will be intermediate between those of adult myxedema and cretinism. Mental development is arrested at the stage at which the deficiency appears. The same is true of osseous development (175). The various descriptions of human cretins do not completely agree in all respects. It is obvious that there are many modifications due to age at time of onset as well as severity of the deficiency. Some of the characteristic symptoms which appear to be of the most interest because of a possible analogy in beef cattle are presented. These symptoms are listed under various headings in order to avoid as much confusion as possible.

Skeletal:

The characteristic lesion is failure of bone formation in cartilage. The long bones, although short, are relatively thick, with prominent muscular ridges. The epiphyses commonly unite late. This marked delay in the processes of maturation is one of the most definite characteristics of hypothyroidism (62, 112, 170, 172, 206, 240). The thickened long bones are often bowed. The expansion of the cartilage end of the long bones is responsible for the marked bending of the ribs (63, 168, 240). The hands are broad, thick and stumpy. The fingers are square at the tips (63, 206).

The feet appear to be broad and squat (63, 167, 206) and the neck is short and thick (63, 240). Some extreme cases also show lumbar lordosis (189) and the individuals are actually deformed (168). When the deficiency has existed from an early age, infantile proportions of the

upper and lower skeletal segments persist, the naso-orbital configuration is undeveloped, and osseous development is retarded (242). If the deficiency does not develop until later childhood when a more mature skeletal development already has been attained, the characteristics of early infancy are not found. Marked retardation of osseous development is not in itself diagnostic of hypothyroidism and may be found in pituitary dwarfism or even in cases of delayed adolescence.

Epiphyseal dysplasia has been considered by some workers as one of the most important anatomic characteristics of hypothyroidism (69, 83, 172, 189, 214, 228, 240, 241, 242). It is due to a disorder of cartilages of the epiphyses and round bones leading to irregularities in their subsequent ossification. Normally, ossification begins from a single small focus in the center of the cartilage and extends peripherally in an orderly manner. If thyroid deficiency exists during the period in which ossification normally occurs, the appearance of the deposition of calcium is considerably delayed. When calcification finally occurs, it appears as multiple, small, irregular foci scattered over a considerable area of cartilage. These grow larger and coalesce to form a single irregular center. According to the stage of the process, the roentgenogram may show multiple small centers of ossification or a single center which may appear either stippled, porous, fluffy or fragmented. Although hypothyroid epiphyseal dysplasia is observed most frequently and is most spectacular in the heads of the femurs and the navicular of the tarsus, it involves all the endochondral centers in which ossification normally occurs during the period in which the deficiency exists (240).

In endemic cretinism, the retardation of ossification is much more irregular than in childhood myxedema. There is a premature synosteosis between the os basilore and the sphenoid with a consequent earlier closing of the fontanels. In myxedema, the enchondral and periosteal ossification is considerably retarded and takes place later in life. The fontanels remain open for a long time (83).

Only those centers show dysplasia in which the appearance of ossification has been delayed as a result of hypothyroidism. With continued treatment, ossification takes place normally in those centers which ordinarily would not have been ossified at the age when therapy was begun (241).

Deformity of the vertebral bodies in hypothyroidism appears to develop in postnatal life. Proliferation of cartilage is irregular and often deficient in cretinism, gargoylism and achondroplasia, and is probably the essential abnormality which permits the formation of these dysplastic vertebrae (69).

The skull is changed in shape since the base is formed in cartilage. The usual picture is that of a brachycephalic head with a broad face and possibly a small sella turcica (77, 115, 168).

The proportions of the head change during gestation. Head length slowly and gradually increases in proportion to width of forehead and also in proportion to width of head at the level of the eyes (227).

The normal changes in proportion of the head in the infant and later during childhood are marked. They are the results of both environmental and genetic factors. The genetic factors, however, seem in the long run to determine the head form of the adult (49).

A definite relationship appears to exist between menarcheal age (a measure of sexual maturity) and size and development of head. In both length and width of head, most markedly in the latter, the dimensions are larger in girls with early menarche than in girls with late menarche (80). Maximum growth tends to occur about the time of menarche; hence, earlier in girls of early menarche. Sex differences for head length and width are much smaller in young children than in adults. The cephalic index increases rapidly from 1 through 7 months, remains approximately level until 10 months, and then decreases very slowly after 12 months of age (11). The head may continue to grow until 50 years. This indicates a more or less continued plasticity with a possibility of prolonged constructive changes before the set-in of senility (105).

In the cretin, the bridge of the nose is flat and broad, causing the eyes to appear widely spaced (63, 170, 240). The head is often asymmetrical (206) and may appear large in proportion to the rest of the body (63, 112, 168, 172, 240). The nostrils are often large and the nose pug-shaped (63, 168). The forehead is low (63), lower jaw prognathic (168), and the palate may be high and arched (167, 168). The forehead is often wrinkled and the palpebral fissures are horizontal (206). The lower lip is thick and may be everted (63, 168, 206, 228). The face appears puffy (63, 82, 228). Macroglossia, together with an open mouth and drivelling, gives the individual a stupid expression (63, 82, 168, 206, 228, 240).

Neural:

The association of mental defect and thyroid insufficiency indicates the close interdependency during growth of the central nervous system and the thyroid gland.

Three varieties of nervous symptoms in cretinism have been described (95, 121):

a. Choreiform
b. Ataxic
c. Spastic

The cretin has an expression that has been described as dull, apathetic, and immobile (81, 170, 206, 240, 242). The individuals are mentally retarded and have other neurological disorders (74, 81, 82, 95, 112, 121, 133, 144, 172, 189). The movements are clumsy and unsteady and they occasionally have cerebral diplegia, affecting chiefly the legs (128). Some suffer from convulsions when young (63) and others have tonic spasm and rigidity of facial and laryngeal muscles (229). Hearing is impaired (150, 155, 168). An extensive biometrical study was made of the endocrine organs in relation to mental disease (176). These results indicated that the insane and mentally deficient people are undersize, both in stature and body weight (46). Their gonads and thyroid are smaller than normal in relation to total weight of the endocrine system while the thymus and parathyroids are larger (176).

A study of the brain of the cretin has indicated that the convolutions of the brain in the parietal and occipital regions are unusually narrow (63). It has been found that the calcium content of the brain is above normal, the phosphorus content below normal. Moderate hydrocephalus has also been noted in the cretin (168, 214). In some, the hydrocephalus appears to be due to a disturbance of the normal relationship between the brain stem and the floor of the skull. In others, the hydrocephalus is due to

constriction of the sigmoid sinuses or obstruction in the posterior fossa (168). In the human, some types of hydrocephalus are inherited as a simple recessive (74). Stricture of aqueduct of Sylvius causes about half the cases of hydrocephalus in infants. Congenital strictures may also occur in the foramina of Monro, the foramina of Mogendie and Lushka, or the cisterna along the base of the brain.

Eyes:

Defective vision appears to be very common in cretins and probably in parents of cretin children (162). Coarse nystagmus and internal strabismus have been noted (150) as well as high myopia and hypermetropia (162, 240).

Teeth, hair and skin:

The teeth are generally retarded and often defective (63, 81, 170, 240, 206). The skin is dry and scaly; in some cases it even appears leathery (63, 82, 170, 206). The hair is harsh, coarse, and usually scanty (74, 170, 206). Onycholysis, the partial separation of the nail from its bed, has also been noted (74).

General health:

The prominent and bulky abdomen is characteristic of the cretin (63, 206, 240). Infants take feeding slowly and with difficulty (170). Many of the cretins are anemic (170) and lowered urine elimination, together with slight albuminuria, has also been noted (129). The respiration is slow and grunting (63), and hay fever and asthma have also been reported (204). The BMR is affected as shown by a slow pulse (63, 240), subnormal temperature (63), hypercholesterolemia, and diminished PBI (242). Some obesity may be present (82) and the peripheral circulation is impaired (242). In some cretins, the thyroid gland is actually impalpable (206).

Other:

The cretin is often small at birth, although the weight is usually within normal limits (63, 82, 112, 172). The voice may be coarse and harsh (240). Excessive fat deposits are frequently found in the posterior triangle of the neck (83, 206). Another cretin characteristic that has been reported is a prominence of the antithenar eminence over the situation of the os pisiformis. This prominence is immediately adjacent to the groove which separates the palm of the hand from the forearm. It is distinctly localized to this portion of the antithenar eminence and, viewed from the above groove, gives a bayonet-like appearance. It probably represents over-development of the small muscles of the inner border of the hand attached to the os pisiformis, as well as, perhaps, an enlarged condition of the bone itself (83).

Adult hypothyroidism:

In adults, many of the familiar physical signs of hypothyroidism depend on a lowered rate of metabolism and alterations in the circulation. In addition, abnormalities in chemical processes of the body are responsible for some of the characteristic changes in subcutaneous tissues, skin, hair, and muscle to which the term myxedema has been applied (240).

The characteristics of adult hypothyroidism may be useful both in accurate classification of dwarfs and in possible identification of transmitters. Some of the characteristic symptoms of adult hypothyroidism are (129, 130, 155, 175):

1. Mentally dull; drowsy most of the day and fall asleep as soon as they sit down

2. Impaired hearing

3. Slowness of movement

4. Skin is pallid, dry and cold; in severe cases, skin is coarse and thick

5. Hair is dry, coarse, and brittle

6. Myxedema occurs in severe cases

7. Normocytic, normo- or hypochromic anemia is a common finding in severe cases

8. Heart increased in size

9. Heart beat is feeble; bradycardia is sometimes observed

10. No consistent changes in blood pressure

11. High incidence of arteriosclerosis

12. Constipation due chiefly to hypoperistalsis

13. Hypothyroid women have diminished fertility and are often sterile; the incidence of abortion, prematurity, and stillbirth is high in untreated cases and is roughly proportional to the severity of the hypothyroidism

14. Serum cholesterol levels high

15. Phospholipid values are also elevated

16. High serum carotene levels have been found in a number of hypothyroid patients; this may be the result of an inability to convert carotene to vitamin A

17. Serum-protein values are frequently elevated and the cerebrospinal fluid pressure has been found to be increased

18. Of the people affected with adult myxedema, 78-82 percent are females

19. One of the first symptoms is hypersensitiveness to cold

20. In the male, sterility is due to low vitality of spermatozoa

In adult life, thyroid deficiency is not accompanied by conspicuous clinical changes unless it is marked. In infancy and childhood, on

the contrary, even moderate degrees of thyroid insufficiency interfere considerably with normal physical and mental growth. Cretinism develops in degree corresponding to the severity of the thyroid deficiency and the age at time of onset (191).

In attempting to associate adult hypothyroidism with physical characteristics, the following description has been offered (155):

> "The bodily habitus as a whole is more often than not that of a rather squat, dumpy, thick-necked and potbellied variety. We have very seldom seen myxedema in tall, thin subjects. Some degree of slight obesity is likewise present in over 80 percent of the cases."

Other investigators have noted that, in a majority of the cases, families of dwarfs were short of stature (196).

Mongolism:

Mongolism is a form of dwarfism that has some of the characteristic symptoms of cretinism (13). It is a relatively common occurrence, an incidence of 0.34 percent of all births having been reported (175).

Diagnosis:

Forehead is higher and broader in newborn infant. Frontal bones prominent. The eyes are protruding and the palpebral fissure appears more or less slanting. The orbital cavity appears small in relation to the eyeballs and the distance between orbits is less than normal. The face is flat. These characteristics become more pronounced as the individual gets older. At birth the height of the Mongoloid child is within the limits of the normal. There is some retardation during childhood and this becomes very apparent after eight years of age. At birth the circumference of the skull is within limits of the normal, but the skull does not grow nearly as rapidly as normal. Ossification centers in the carpal bones may often be premature.

Study of skull:

The skull is the most important characteristic of the Mongoloid. The anterior cavity is characterized by extreme protrusion of the roofs of the orbits. The cribriform bone is short and retracted and forms a small, deep valley between the arches of the orbits. The roofs of the orbits ascend laterally toward the frontal bone without leaving any deepening between the top and the facies temporalis of the frontal squama. The sphenoid bone is small and the body of the bone underdeveloped. Neither the frontal nor the sphenoid sinus is present. The middle cavity appears deep and is overshadowed by the projecting major wings of the sphenoid bone.

Primarily, the cartilaginous bones are affected. There is a disorder in the proliferation and ossification of the cartilaginous bones. In the carpal and long bones, ossification is early and growth of the bones comes to an early end. At the base of the skull the cartilaginous bones show lack of proliferation and irregularity in ossification. The membranous bones are much less affected than the cartilaginous bones; thus, the latter continue to develop. The closure of the fontanels is usually

retarded and the fontanels are larger than in normal children. The closure of the fontanels is due to proliferation and ossification of membranous bones.

Early ossification of the base of the skull limits the growth there, whereas the membranous formation of the temporal and parietal bones will probably result in an increase in width. Increase in length is more limited, and the skull becomes more brachycephalic because the occiput does not participate in growth.

The malformation of the skull in Mongolism resembles that of chondrodysplasia, but in chondrodysplasia only the base of the skull is affected and the vault does not participate in the disorder. In cretins also, the vault is normally developed and the skull is usually larger in circumference than normal.

In one of the early studies of Mongolism and cretinism, the following characteristics were listed as typical of Mongolism (83, 206):

1. Noticeable from birth
2. Skull brachycephalic; contour rounded or short oval
3. Forehead usually smooth
4. Palpebral fissures "almond shaped"; frequent epicanthus and strabismus
5. Cheeks chubby
6. Lips often transversely fissured
7. Tongue large and coarsely papillate
8. Skin smooth in infancy but furfuraceous later
9. Hair "wiry"; downy growth common on forehead and cheeks
10. Thyroid gland palpable
11. No excessive fat deposits in posterior triangle of neck
12. Long bones shorter than normal, but slender
13. Hands broad, thumb and little finger short; fingers taper at ends
14. Feet large and flat; fissure between great and next toe often seen
15. Abdomen often distended; occasional umbilical hernia
16. Expression more or less vivacious and mobile

Some additional characteristics that have been described are:

1. Replacement of the usual three creases on the minimal digit of the hand by two creases only, so that the markings on this finger resemble those on the thumb, although the correct number of phalanges is present (177)
2. Strabismus (137)
3. A deep furrow between first and second toes of both feet (137)
4. Brain in Mongolian idiocy shows (50):
    a. Agenesis - as evidenced by cell poverty and failure of gyral development
    b. Aplasia - as shown by its small size in comparison with normal
    c. Paragenesis - as demonstrated by the frequent occurrence of anomalies

Members of a series of over 100 families, each selected by the presence of at least one case of Mongolism imbecility, have been blood typed for several factors. No gross anomalies in the distribution of antigens either in the propositi or their sibs were observed (127).

It was therefore concluded that Mongolism cannot be due to antigenic incompatibility between mother and fetus for any of the antigens studied. In a review of the causation of Mongolism and its prognosis, it was determined that 16 percent of the cases had a definite neuropathic family history (66).

There is a definite opinion among many research workers that a maternal influence is directly associated with Mongolism (111, 115, 175, 199, 206). More than a third of the Mongoloid children have congenitally missing or defective upper lateral incisors. This is interpreted as evidence of injury to the primordium normally differentiating about the seventh, eighth or ninth week of intra-uterine existence. The Mongoloid baby is thought to have suffered critical stress at this period of life and to have survived, but with the permanent arrest of certain ocular, dental, cardiac, skeletal, and nervous tissues (111).

The factor or factors causing this disturbance have not been definitely determined. Some which have been postulated are:

1. Glandular or chemical disbalance in the mother at the time of gestation (199)
2. Too narrow amniotic sac or too high a pressure inside it (115)
3. Imperfect nidation due to a defective uterine mucus membrane (115)
4. The age of the mother may be a factor, older mothers tending to have a higher incidence (206)
5. Later children in large families are more generally Mongoloid (206)
6. Uterine exhaustion; ill-health, privation, or anxiety of the mother may be involved (115)
7. Miscarriage (115)

In the bovine, the uterine part of the placentoma is an outgrowth from the stratum compactum of the caruncle. It forms crypts which surround the villi of the fetal cotyledon. A low syncytium of undetermined origin covers the septa of the caruncular crypts everywhere except on their distal ends. This syncytium contains a lipid and it forms a complete alkaline phosphatase barrier between maternal and fetal bloods (238). The fetal effect must be transmitted through this barrier, just as maternal influences are carried to the fetus. However, the relationship can be more complex than a straight fetal-maternal exchange during gestation. For example, it has been shown that eggs of goitrous female pigeons take two to three days longer to hatch (74). There are also reported instances of Mongolism in one of twins (169) and it has also been postulated that it may be caused by the father since two brothers who married unrelated females each had a Mongoloid child (137).

Gargoylism:

Gargoylism is considered as a form of dwarfism different from cretinism and Mongolism. The characteristic symptoms of gargoylism have been described in some detail (64, 100, 116).

Most cases grow normally for about the first year, then growth is markedly retarded.

TABLE 6. Comparison of Mongolism and cretinism (175)

	Cretins	Mongols
Condition apparent	3 to 5 mos. of age	At birth
Height	Dwarfs	Normal
Body proportions	Short extremities	Normal
Hands and feet	Square; short	Short; bifid tendency in hands and feet
Closure of fontanel	Greatly delayed	Some delay
Teeth	Delayed eruption	Some delay in eruption
Joints	Normal	Extremely flexible
Skin	Dry, doughy, thick	Soft, shiny, smooth
Color of face	Pale yellow	Red
Perspiration	Lessened or absent	Normal
Hair	Sparse, brittle	Fine, soft
Eyelids	Pseudo-edematous; thick	Slit, turned up and out
Nose	Bridge depressed	Wide, depressed
Mouth	Thick lips, large tongue	Normal size, fissured tongue, usually protruding and with small tip
Expression	Apathetic or anxious	Cheerful, comic, or stupid
Heart	Slow rate	Frequently congenital malformation
Speech	Delayed; deep voice	Delayed
Effect of thyroid therapy	Rapid improvement of all symptoms	Improvement of constipation, hernia and dentition only
Infections	Normal resistance	Very susceptible to disease

Head:

The cranium is nearly always enlarged and, unlike the face, its conformation is variable. Scaphocephaly, acrocephaly, oxycephaly, and brachycephaly have been noted.

Bulging of the squamous part of the temporal bones often occurs. Hydrocephalus is a frequent complication. Bony ridges along the suture lines and unduly prominent supraorbital ridges sometimes occur. Closure of the anterior fontanel is always greatly delayed.

The facial appearance is typical and one of the most constant features. The nasal bridge is flat and wide and the nostrils are often turned forward. The mandible is broad and heavy and the teeth are widely spaced, irregular, and poorly developed. Dentition is often greatly delayed. The lips are thick and the tongue large. Full cheeks are the rule and they often have a ruddy hue. Ears appear unduly low-set and occasionally are enlarged. Hair is firm and silky.

Trunk:

Neck short, head appears planted on the shoulders. Chest usually malformed.

Vertebrae:

In almost every instance, kyphosis in the lumbar or dorsilumbar region has been noted, usually associated with scoliosis. Vertebral bodies are irregular, flattened, or wedge-shaped in outline and may be considerably reduced in size. The twelfth dorsal or first or second lumbar vertebra is most affected, and in this region one or more of the vertebral bodies has an anterior hook-like process.

Limbs:

Arms relatively short; mobility of joints impaired. Scapulae usually lie abnormally high. Bones are thickened and roughly formed, the latter being most apparent in the neighborhood of joints. The humeral and femoral heads are irregular and flattened, and the glenoid fossae and acetabula unduly shallow. Irregular epiphyseal ossification is a constant feature, osteosclerotic and rarefied patches often being seen. Carpal ossification is retarded.

Brain:

Morbid condition; simple, convolutional pattern. Internal hydrocephalus noted. Cortical nerve cells sparse, and degenerative changes in the nerve cells seen throughout the central nervous system.

Dentition:

Delayed. Teeth irregularly spaced and wide apart.

Corneal opacities:

Diffuse dystrophy of cornea, consisting of multiple opacities scattered throughout the cornea, but situated principally in the deeper layers.

Abdomen:

Enlargement of liver and spleen, or of one organ alone described in a majority of cases.

Mentality:

Mentally defective - actual regression may occur.

Biochemical tests:

1. High blood-glycogen
2. Creatinine and cretaine excretion normal
3. Serum calcium, blood phosphorus, and phosphatides not abnormal
4. Response to thyroid therapy is temporary and minimal

Other tissue:

1. Widespread lipoid infiltration of liver, anterior pituitary, and lymph glands noted in some cases
2. Thyroid has the structure of hypothyroidism
3. Rhinitis occurs in a majority of the cases
4. Deafness and hypertrichosis common

The usual forms of gargoylism are apparently inherited as a simple recessive (116), although a group with typical symptoms of gargoylism, except that corneal opacity was lacking, appeared to be inherited as a sex-linked recessive (159).

Other types of dwarfism:

Dwarfs who remain sexually infantile probably have a pituitary defect involving not only the growth hormone but gonadotropic and other hormones. These patients may be of normal size at birth and grow normally during the first few years of life. After this, growth may become very slow but rarely ceases. There is usually considerable delay in epiphyseal development which may not be as marked as in hypothyroidism, but epiphyseal dysplasia does not occur. The skeletal proportions and the features do not remain as infantile as in hypothyroidism and there are not the sluggishness, circulatory impairment, and other signs characteristic of hypothyroidism. Some pituitary dwarfs are subject to hypoglycemic attacks which are probably due to deficiency of adrenocorticotropic hormone (242).

It is exceedingly difficult to prove the pituitary origin of dwarfism during childhood.

I. Pituitary dwarfism with detectable lesion of pituitary gland (175).

  A. Lesion can be recognized clinically by roentgenograms
  B. Clinical characteristics:
     Arrested growth, dwarfism, with persistence of infantile body proportions as of the age when growth was arrested
  C. Hypogenitalism
  D. Growth:
     Growth arrested at time of destruction of pars distalis--further growth does not occur or is minimal, body proportions remaining at the stage corresponding to the age at time of arrest; no mental retardation as in hypothyroidism

II. Pituitary dwarfism with no evidence of lesions of the pituitary
Minimal requirements:

  A. Infantile proportions
  B. Retarded epiphyseal development
  C. Hypogenitalism
  D. Absence of mental retardation or other signs of cretinism

Hereditary dwarfs are generally recognized as belonging to two distinct types (74):

1. Achondroplastic (chondrostrophic) and
2. Ateliotic

The former have a trunk of normal length, short legs, and large joints, their defect being in the cartilage formation at the epiphyses. The latter are miniatures of normal proportions due to growth practically ceasing at an early age in childhood.

Achondroplastic dwarfism (in humans) appears to be generally, if not always, a simple dominant in inheritance. Ateliosis is, at least in most cases, a simple recessive.

In ateliotic dwarfism, the infant is of normal size at birth, but growth is very slow, and is usually suspended early, although it may not be complete until thirty years of age. The face is flat, the features babyish, the hands and feet small. The height seldom exceeds 40-45 inches. They may also be achondroplastic. There is often cryptorchidism, delayed dentition, and irregular teeth. These little people, although normally proportional, are too frail and too frequently sterile to form a race under any circumstances, but they sometimes live to extreme old age. Although they are frequently of normal or acute intelligence, and sometimes highly accomplished, they may also be of dull or defective intellect. The deficiency is of a hormone of the anterior pituitary, produced by the acidophile cells (101).

Deficiency of the anterior lobe of the pituitary gland in early childhood can manifest itself in the following dentofacial conditions (193):

1. Lack or delay in development and growth with marked retardation in the cranium and face

2. Delay in eruption; prolonged retention, and partial ankylosis of deciduous teeth with retardation of formation and eruption of permanent teeth

3. Persistence of juvenile dental characteristics

4. Tendency toward development of deep overbite

5. Crowding of teeth--in some cases teeth are small and crowding is not present

Complete physical descriptions were made of 53 adult male and 31 adult female midgets (57). As a result of this study, the individuals were divided into three morphological groups:

1. Fetal-like midgets
2. True midgets
3. Minitatures

Certain characteristics of the face and head appear to be almost universal among midgets:

1. Thin lips
2. Fine hair texture
3. Scanty eyebrows
4. Bulging temporal regions
5. Large ear lobes

"Primordial dwarfism" has been described as characterized by no retardation of developmental processes or other manifestations of endocrine deficiency (242). The patient is usually small at birth and growth is slow from infancy. Epiphyseal development and sexual maturation take place normally at about the usual time and the features mature during adolescence. The child develops into a miniature adult.

A syndrome, characterized by primary ovarian insufficiency and decreased stature, has been reported (2). They are differentiated from pituitary dwarfs by the following criteria:

1. Individuals short rather than dwarf
2. Bone ages only slightly retarded
3. Estrin therapy leads to improvement
4. Patients strong and well nourished

DWARF DESCRIPTIONS - SMALL ANIMALS

A recessive type of dwarfism has been studied in a stock of black silver mice (210). The dwarf mice attained about one-fourth of the weight of their normal sibs. Up to the fourteenth day of age their growth rates were normal. At twelve or thirteen days of age, their tails and noses were noticeably shortened. They were small, sub-normal in vigor, and both males and females were sterile. A study of the endocrine glands of these dwarf mice showed that the thyroids were extremely reduced in size (208). The glandular tissue was separated by adipose and connective tissues. Some of the thyroid tissue was not organized into follicles and contained little or no colloid. The adrenal cortex was reduced in thickness and the characteristic zonation absent or indistinct. The gonads, although delayed in development, did not show profound aplasia. The anterior pituitary was markedly abnormal; no eosinophiles were present. Daily implants of fresh rat anterior lobe into the dwarfs resulted in positive improvement in all cases. In appearance, the treated dwarfs could not be distinguished from normal mice. They attained sexual maturity; their adrenals, testes, and thyroids appeared normal. The anterior lobe of the pituitary remained the same as the untreated dwarfs.

It was also shown that this hereditary dwarf mouse and hypophysectomized rats manifested similar conditions (209). In almost all characters the two types are similar; however, one outstanding difference between the hereditary dwarfs and the hypophysectomized rats was the degree of development of their reproductive systems. In hereditary dwarfs the testes and the motility of the sperm were not greatly different from normal. In hypophysectomized rats the testes became flabby, the sperm did not develop and the seminal vesicles and other glands became greatly reduced in size. The ovaries of hypophysectomized rats were smaller in size than those of hereditary dwarfs. The uteri of dwarfs were infantile, whereas the uteri of hypophysectomized rats were thread-like. This suggested that the pituitary growth hormone of the hereditary dwarf was suppressed without a corresponding suppression of the gonad-stimulating hormone.

A careful study of the eosinophile cells present in the anterior pituitary of this strain of mice indicates that the dwarf has none and that in the heterozygote they may be intermediate in number between dwarf and normal genotypes (51).

A detailed description of some of the metabolic features of the anterior pituitary dwarf mouse indicates that in many respects it is very similar to a cretin-type dwarf (165). The reduced growth in the dwarf is first apparent in the second week. The dwarfs remain small and their weight hardly exceeds one-third that of their normal brothers and sisters. The shape of the head is broader than is normal. The nose is short and blunt, the ears small and rounded. The posture differs from the normal, the dwarfs being more crouching, short, and almost spherical in appearance, in contrast to normal mice which are rather long and slim. The gait is slow and stilted. The coat is not smooth, thick and glossy as in normal mice, but more ragged, thinner and almost dull. Metabolism is considerably

TABLE 7. Aids in the diagnosis of dwarfism (242)

	Degree of Dwarfing	Epiphyseal Ossification and Fusion	Skeletal Proportions	Features	Sexual Development	Special Characteristics
Hypothyroidism	+++	Marked Retardation	Infantile	Infantile "Cretinoid"	Late with incomplete maturation	Epiphyseal Dysgenesis High cholesterol, etc.
Delayed Adolescence	+	Moderate Retardation	Normal	Immature	Retarded but eventually normal with late growth spurt	None
Pituitary Dwarfism	+ to +++	Retardation	Normal	Immature	Remaining infantile	F.S.H. low 17 - K.S. low
Primordial Dwarfism	+ to +++	Nearly Normal	Normal	Mature	Normal maturation	Otherwise Normal
Ovarian Agenesis	+	Nearly Normal	Normal Boyish	Mature	Female organs infantile	F.S.H. high 17 - K.S. low
Sexual Precocity	+	Premature	Short Lower Segment	Precocious Mature	Precocious	F.S.H. normal 17 - K.S. high or normal
Progeria	+++	Normal	Mature	Old Wizened	?	Slender, Emaciated, Bird-like Features

reduced, being only 60 percent of the normal. The mice eat well and are able, when they are about a month old, to manage without their mothers provided the temperature is suitable. They are sensitive to cold and succumb easily if the temperature in the cage drops below 20 to 22 degrees centigrade.

The dwarfs, moreover, are sterile. Their sexual organs are not absolutely infantile but the testes and ovaries attain only a certain slight degree of development. Castration produced distinct changes in the secondary sexual characteristics. The anterior lobe of pituitary body is hypoplastic with complete or almost complete lack of eosinophile cells. The thymus is comparatively small; the thyroid gland presented distinct and, in part, very widespread fatty degeneration of the epithelium; no typical differentiation of the cell strings was found in the parathyroid gland, the cells being small with a slight amount of protoplasm; the testes and ovaries were only slightly developed; the medullary part of the suprarenal gland was normal while the cortex was somewhat small; zona fasciculata was especially small, and zona reticularis especially defective in development. The pancreas seemed normal in young dwarfs but was found to be pronouncedly atrophied in the older animals.

The livers of dwarf mice contained very abundant quantities of glycogen, more than that of normal animals; the fat content, on the other hand, was scanty in the dwarfs while normal mice had very abundant quantities of fat in the livers. If the animals were starved, it was found that the glycogen in the normal mice was rapidly and almost entirely mobilized, contrary to the fat which diminished only slightly. The dwarfs seemed to be able to mobilize easily the little fat they were capable of depositing but they were not able to mobilize the glycogen deposits in the normal way. The dwarf mice were more sensitive to insulin than the normal ones (165).

A different type of dwarfism in mice, called "pigmy", has also been described (120). These mice are smaller than normal at birth, but some do overlap with normals. Growth is similar to normals but at a very reduced rate. The condition can be recognized at twelve days of age. In appearance, the adult has short ears and feet, but the tail is long. The coat appears well groomed, and in general the mouse has the appearance of a sleek, streamlined animal. They are as active as normal animals but both sexes are sterile. The condition is due to a simple recessive gene.

Recently, a new dwarf mutation in the house mouse designated "agitans" has been described (102). Mutants can be recognized from ten days onward. They have progressive arrest of growth, restlessness, generalized tremor, and ataxia. Some mutants are underweight from birth. Growth arrest and other symptoms are of variable intensity. Some animals are much more affected than others and these usually become cachexic and die when they are 20 to 30 days old. Their weight is one-half or less than that of normal sibs. Those that live beyond this critical period are subject to diseases such as digestive troubles or parasitic troubles, which apparently do not affect their normal sibs.

Ataxia and restlessness become manifest when the mutants begin to walk. They walk hurriedly with a stiff-legged, "insect-like", pace, and very often they fall over on their sides or hind legs. After one month, their gait changes and they walk with a "duck-like" waddle, the legs being held wider apart than in normal mice.

Tremor, the most prominent symptom, is apparent at ten days. A fine trembling of the whole body--it may disappear during rest--becomes more marked as the mutants grow older. The condition is due to a simple recessive gene. The main pathological finding is an atrophy of the Purkinje cells in some regions of the cerebellum.

A study of the effectiveness of selection for body weight in mice has shown that the frequency of a dwarf gene can be greatly modified in a relatively short time (134, 236). The investigators selected within groups for small, medium, and large body size. No dwarfs were born in the foundation stock and, in the first generation of selection for small body size, one dwarf was produced. No dwarfs were ever produced in the medium or large size groups.

In the small size group, three of the four inbred lines produced dwarfs. The frequency of dwarfs increased to the third generation and thereafter tended to remain at a high level. In the third to the fifth generations, 15.5 percent of the mice raised were dwarfs. It seems probable that the original stocks carried the dwarf gene in low frequency and that it had some effect in the heterozygous condition. Selection for small size increased its frequency. It appeared that the heterozygous individuals were enough smaller on the average than homozygous normals to have approximately twice the chance of being selected for breeding purposes and producing offspring.

It has also been shown that races of mice selected for body size alone differ strikingly and significantly for other traits as well (141). The large race had a different color, was more docile and inactive, had comparatively shorter ears, feet, and tail, and produced many more young per litter. The fact that the brown animals were larger was believed to be due to the action of the genes for size causing brown color rather than a linkage (35).

Hydrocephalus has been studied in mice (37). Young mice may show a swelling of the head at birth but the character does not become noticeable until a week or two later. A bombose skull was caused by the pressure of the clear liquid which collected above the brain and distended the roof of the skull outward. The brain itself tended to be pushed downward and forward. It is due to a recessive gene, lethal in homozygous form, and may be linked with "flexed tail."

Another type of hydrocephalus has been described in which the mice are also dwarfs (249). The affected animals breathed more rapidly and showed sterility as well as a high infant death rate. Only one-fifth of the affected animals survived to an age of six weeks. The hydrocephalic condition apparently begins in embryos at 11 or 12 days (21). Infiltration of excess cerebrospinal fluid takes place into the connective tissue surrounding the medullary tube. The fluid finally escapes into the brain cavity through the choroid plexus.

Three types of hydrocephalus in the mouse are characterized by a dome-shaped skull (62). The types are variable in growth retardation, but all have a high mortality. There is no apparent prenatal mortality but an excess of females are affected. After 120 days of age, normal mice from hydrocephalic litters were larger than normal mice from completely normal litters.

A maternal effect has also been postulated to account for some abnormal conditions in the house mouse (192). A consistent and significant difference in the in vitro rate of incorporation of methionine into liver protein of two inbred rat strains has been demonstrated. The factors which control the differences in enzymatic activity act through both the individual and maternal genotypes. The inbred F milk influence is able to increase J liver activity to the F level, while the J milk exerts no apparent effect on the F offspring.

Reciprocal hybrids between two strains of mice were found to differ with respect to the incidence of mice with five or with more than five lumbar vertebrae. The hybrids tend to resemble the strain of the female parent (84). One explanation is that the cytoplasm of the ova produced by mothers of the two strains is different. The alternative explanation is that the biological environments furnished by mothers of the two strains to the developing embryos are different.

A dwarf mutation in the rat has been studied (122). The young appear normal at birth, but on the twelfth day differences appear. The dwarfs have hair that is softer, finer, and thinner than normal. The body proportions are comparable to the normal, only greatly reduced in size. They are weaker, less thrifty, and shorter lived than normal, and have a distinct opacity of the eye apparently involving the lens. The investigators consider the condition is not due to the pituitary.

A goiter survey in albino rats shows females more subject than males (151). The incidence for males is 4.5 percent, for females 7.8 percent. There is a higher incidence during the warmer months. It is most frequent at the age of sexual maturity.

A dwarf mutation in the rabbit has been studied in considerable detail (85, 86). The character is due to a simple recessive gene and is invariably lethal in homozygous form. The dwarfs are one-third the size of normal litter mates. The posterior calvarium is rounded and bombose, but its slope breaks abruptly in the supraorbital region, giving the snout a characteristic dished-out appearance. The ears are small and appear to sit abnormally far back on the head. The frontal and parietal bones are calcified only at their inferior borders. Throughout the remainder of their extent they are represented solely by membrane.

A detailed study was made of the transmitters. If birth weight of largest litter mate equals 100 percent, dwarfs weighed 35-45 percent, transmitters 75 percent, and normal sibs 94 percent.

The great majority of transmitters present no consistent external physical alteration other than that of size, but some abnormalities have occurred among known transmitters:

1. Cataracts of the lens and structural variations of the iris appear frequently

2. Kyphosis

3. Internal bowing of forelegs

4. Variation in the calvaria consisting of symmetrically placed defects in the frontal lobes

The authors believe these are probably independent variations and not directly associated with the dwarfism transmitters.

It was noted that the majority of female transmitters became overfat at maturity and unless they were bred at frequent intervals the fat in normal regions accumulated to an abnormal extent. Large deposits of fat were also found in abnormal depots, particularly in the anterior triangle of the neck and about the shoulder girdle.

Fertility of both males and females is high, but litter size is generally smaller than normal.

A disturbance of calcium metabolism occurs in older animals. The bones of the calvarium, especially the parietal bones, are roughened and at autopsy are found covered with deep erosions. The incisor teeth are pitted and frequently are ground down to the gum margin.

Females are particularly susceptible to toxemia of pregnancy in their third or fourth gestation. Older females almost always show adenomata or adenocarcinomata of the uterine fundus. The hypophysis shows pronounced increase in size and number of acidophiles. The increase was generalized throughout the anterior lobe.

Two separate types of recessive achondroplasia have been described in the rabbit (28, 43). In the first type (28) the affected animals die at birth or within a few hours after birth. There was nothing in the normal sibs in growth or maturity to suggest the condition. Transmitters could be identified only by a breeding test. There was comparatively little variation in the general appearance of the achondroplastic individuals:

1. Reduced size
2. Broad, squarish head with prominent calvarium
3. Transverse depression across the base of the nose
4. Small teeth
5. Flat muzzle
6. Comparatively short and flaring thorax
7. Conspicuously large, relaxed abdomen
8. Short, broad, fleshy tail
9. Marked redundancy of the skin
10. Large, fleshy, protruding tongue
11. Occasional folding ears
12. Occasional cleft palate

In second type of recessive achondroplasia in the rabbit, the adult animals are characterized by normal body size but they have short, often crippled legs (43). Externally, the new mutation is first recognizable by a small, cartilaginous papilla arising at the base of the external auditory meatus.

Examination of the skulls of these animals shows the osseous part of the external auditory meatus to project downward and outward instead of upward and backward. This is due in part to the fact that the entire dorsal portion of the skull bends down at a more acute angle than in normal animals. The bend is such that the foramen magnum faces downward, more as in the human skull. At the same time, the mastoid processes and neighboring structures are compressed and twisted, resulting in differences in angularity of the ears.

TABLE 8.--Organ Weights (85).

Organ	Normal		Transmitter		Dwarf	
	Actual weight Mg.	% of net body weight	Actual weight Mg.	% of net body weight	Actual weight Mg.	% of net body weight
Thyroid	6.80	0.018	5.05	0.017	1.90	0.012
Pituitary	2.40	0.006	1.23	0.004	0.45	0.002
Thymus	60.70	0.162	47.30	0.163	31.50	0.196
Liver	2474.50	6.590	1796.30	6.210	947.00	5.910
Heart	250.70	0.668	199.00	0.668	128.00	0.800
Brain	1223.50	3.250	1145.30	3.960	949.00	5.930

A dominant type of achondroplasia in rabbits has also been described (34). The heterozygous rabbits were of reduced body size. Their birth weights were about two-thirds that of normal rabbits, and they remained dwarf throughout their lives. They lived and reproduced, but mating of heterozygotes produced one normal homozygote in every four offspring. The homozygous dwarfs died after birth. They were lighter in weight than the normal rabbits and had an extremely short upper jaw. Because of this, they often died of starvation. It was suggested that the defect is due to reduced activity of the pituitary gland.

A recessive type of dwarfism in guinea pigs has been reported as the first case of hereditary dwarfism in rodents (212). Most of the dwarf guinea pigs died very early and the few that lived were sterile. They did not attain more than half the size of the normal guinea pigs. The shape of their skulls and skeletons was also altered. They were characteristically short of body and legs.

Three inbred families of guinea pigs that show differences in live weight amounting to over 100 gm. have leg bones nearly equal in dimensions (61).

A very complete study has been made of various types of dogs and their hybrids (220, 221, 222). The achondroplastic dwarfs, such as dwarf bulldogs and other dwarf breeds, have a larger thyroid per weight of dog than such normal breeds as the foxhound, while the giant breeds have a relatively small thyroid. In crosses between giants and dwarfs, the F_1 is intermediate in thyroid size, while the F_2 segregates into types with large, intermediate, and small thyroid. In crosses between the dachshund and Boston bull terrier, both with large thyroid, the F_1 thyroid is still larger and segregation occurs in F_2. There are also differences in histological structure.

In general, the amount of thyroid gland per kilo of body weight is greater in dwarfed breeds than in the normal foxhound type. All the oversized or giant dogs have a smaller amount of thyroid gland per kilo of body weight than do dogs of usual size.

The basset hound and the dachshund both have very short legs, typically achondroplastic, the head, body, and tail developing normally; but the

dachshund has a dwarf body while the basset has not. In crosses between the basset and the long-legged types such as the saluki or the German shepherd, the legs of the F_1 are nearly as short as the basset, the F_2 showing a 1:2:1 segregation for a single factor. In the Asiatic Pekingese and other breeds, short legs are also dominant.

Localized achondroplasia of the head of the bulldog appears to result from a combination of several recessive elements, as shown by crosses with the dachshund. In the F_2 such disharmonic types as a long upper and short lower jaw may appear. F_1 between normal head and bulldog is intermediate but closer to normal type. The face is shortened and the region of the nose is decidedly depressed. The zygomatic arch is more strongly curved than is usual in the long skull and the lower incisors project beyond the upper, giving a slight degree of undershot jaw. In basset-bulldog crosses, the head and tail skeleton are distorted as in the bulldog and leg skeleton as in the basset. The factors for local achondroplasia are independently inherited.

As a result of man's deliberate preservation of practically every newly merged mutation of dogs, excluding those that are impossible for him to maintain because of the animal's poor chance of survival, the dog has become the most varied domestic species of animal on the earth.

There are numerous cases of dwarfism in dogs, but little work has been done on the inheritance of this trait in this species. The ateliotic dwarfs, or midgets, and the achondroplastic dwarfs are common in dogs. Some dogs exhibit typical complete dwarfism; others have normal trunk with achondroplastic legs; still others have normal legs but achondroplastic heads and abnormally abbreviated caudal skeletons.

The important examples of achondroplastic dwarf breeds are:

a. Asiatic Pekingese
b. French bulldog
c. Boston terrier
d. Basset hound bulldog
e. Dachshund

An achondroplastic condition designated as "creeper" has been described in the domestic fowl (44). These fowl were called Dumpfries or Creepers in the Old World, and Creeper or Brevicrews in America because of their unusually short legs. Their legs and wings are abnormally short but they are rather normal in other respects. They have the appearance of sitting even though they are standing. They are of various colors--barred, blue, black, buff, white or frizzled.

All of the long bones of the wings and legs are abnormally short. The tibia of the leg is short, bent and not fully developed, but the fibula is overdeveloped. In this respect, creepers differ from all known breeds of fowl. In modern birds and in fossil forms, the tibia is the main support of this part of the leg with only a small splint to represent the fibula. Because of the abnormalities of the legs, creepers, when trying to walk, make a "lizard-like" movement with both legs and wings which is "strongly atavistic in character."

Genetic studies of the creeper fowl have been reported (56). A mortality rate of 45.5 percent of the embryos from creeper inter se matings during one to six days of incubation was found whereas it was only 4.2 percent

from the matings of creepers with normal fowl. The mortality rate at other periods during incubation was about the same for both types of matings as shown in Table 9. The large difference in percentage of eggs hatched between creeper inter se matings (27.3 percent), and the mating of creeper with normal birds (66.2 percent), under the same environmental conditions, was due largely to the death of homozygous creeper embryos at an early stage of development. Therefore, all creeper chicks which hatched were heterozygous for the creeper condition.

Subsequent investigation substantiated these earlier views (124). The results also indicate that the heterozygous creeper condition is less viable than the homozygous normal genotype. The study of the creeper embryos at the time of death showed:

1. Creepers have shorter heads (do not overlap with normal).

2. Posterior body length of creeper fowl is also shorter but not as definite as head length.

3. Organ formation is more nearly normal in creeper embryos than is growth.

4. Lethal action appears to be brought about by cessation of growth, not by some gross malformation.

A recessive type of dwarfism has been described in Rhode Island Red pullets (123). The retarded growth of the dwarfs was recognizable at two to four weeks of age. The outer toes were usually curved outward and backward. The legs were short. They had bulging eyes, disproportionate growth of the skull, "parrot-beak", swollen tongue, dry skin, and short tarsometatarsus. The sacrum was small and high so that the tail appeared to be abnormally high on the body. They had fewer marrow cells in the long bones and the thyroid glands were enlarged. None of them was sexually mature. Because of its resemblance to thyrogenous dwarfism in humans, the condition was named "myxedema infantilis".

This same condition has also appeared in other flocks and has been studied by other investigators (149, 234, 235). The dwarf birds could be identified at about two weeks of age because of their short-leggedness, curved toes, and "parrot beaks". They were not distinguishable at hatching time. They did not live as long as normal birds. They were given the best possible feed and care, but were very susceptible to colds, bronchitis, and other diseases. Some became paralyzed.

A few of the "carriers" of dwarfism could be identified by appearance prior to breeding test while others could not be identified without the progeny test. The egg production and egg weights records indicated that the "carrier" birds had normal production qualities. It was suggested that this was a cretin type of dwarfism.

A recessive chondrostrophy in Rhode Island Reds is reported as probably due to faulty calcium metabolism (99). The affected birds have wide, flat heads with both mandibles greatly shortened. The long bones of the upper and lower limbs are shortened and thickened in the humerus and ulna, with extreme thickening in the tarsometatarsus. They have greatly distended abdomens.

TABLE 9.--Results of mating creeper fowl inter se and with normal fowl (56).

	Fertile Eggs	Dead Embryos 1-6 days	Dead Embryos 7-13 days	Dead Embryos 14-21 days	Hatched
Creeper male x Creeper female	33	15	5	4	9
Percentage	100	45.5	15.2	12.1	27.3
Creeper male x Normale female	71	3	12	9	47
Percentage	100	4.2	16.9	12.7	66.2

An inherited shortening of the long bones in the turkey has been described (5). It is due to a simple autosomal recessive. Hatchability was very much reduced. The heterozygous mature hens had slightly but significantly shorter tarsometatarsi than normal hens of similar weight.

In a study of the inheritance of thyroid size in the dove, genetic factors for thyroid size have been demonstrated (186). Body weight was not necessarily associated with thyroid size.

DWARF DESCRIPTIONS - DOMESTIC ANIMALS

Dwarfs in cattle have been recorded since 1860 (203). Dwarf types have been reported from many breeds, including (a) Aberdeen Angus, (b) African Uganda (Zebu), (c) Ayrshire, (d) Dexter, (e) Guernsey, (f) Hereford, (g) Holstein-Friesian (American, British, Swedish), (h) Jaroslav, (i) Jersey, (j) Oplandske (Norway), (k) Shorthorn, (l) Swedish Red and White, (m) Spanish (Puerto Rico), (n) Telemark, (o) West African Shorthorn.

The "bulldog" calves of the Dexter breed in Ireland were described in detail in 1904. They have short, round heads, depressed nostrils, bulging foreheads, projected mandibles, flabby tongues, short vertebral columns, thick, loose skin, inguinal hernia, and short legs. They are about half normal size. They are aborted between the sixth and eighth month of the intra-uterine period. The dam has an accumulation of uterine fluid between the fourth and fifth month of gestation. Breeding tests showed that the condition is inherited as a single autosomal dominant (110).

The Dexter cattle are heterozygous. Inter se mating of Dexters results in segregations in the ratio of 1:2:1 (25 percent of the offspring being homozygous normal Kerry type, 50 percent heterozygous Dexters, and 25 percent homozygous Dexter monsters). No bulldog calf was produced from the mating of Dexters with Kerry cattle.

"Duck-legged" cattle, which appear to be similar in appearance to the Dexter breed, have been reported in the United States (139). No dwarf or "bulldog" calves were found among the progeny of the "duck-legs". Some of the "duck-leg" cattle were confused with short-legged cattle of conventional breeding. The pituitaries of the "duck-legs" were unusually small.

The trait was due to a single dominant gene, although dominance is sometimes incomplete.

Hereford breeders developed a small-type cattle which were placing high in the show rings (246). They were short-legged and early maturing. These cattle were generally less extreme than the Dexter type, but were smaller at maturity than conventional Herefords.

"Compact" Shorthorns were described that resembled the small-type Herefords (223). They could be identified at birth and the characteristics were distinct throughout life. They appeared shorter of head, neck, body, and legs than the "standard" type of Shorthorn cattle. They appeared to be thicker in their muscles. Some of them had a tendency toward heavy shoulders and crooked legs.

Although they weighed less at maturity, they exhibited a good beef conformation. They were favored by some purebred and commercial breeders, and they were popular at fat steer shows. It was noted that since 1936 the "compact" type of cattle had been winning the major prizes in fat steer shows and in carcass contests. From field data available, it was concluded that the "compact" condition in Shorthorns is due to a single dominant gene. An investigation was made of the nutrient utilization by Shorthorn steers of "compact" and "conventional" type (237). They found that (a) the "compact" type was less efficient than the "standard" type Shorthorns in the utilization of dry matter during growth, (b) the "compact" type required 70 days less time on feed than the conventional type to reach choice grade, (c) all carcasses were graded choice, and (d) the conventional type cuts were somewhat fatter, but that the "compact" type cuts were heavier in bone.

Dominant achondroplasia has also been reported in British Friesians (15) and in Jerseys (154).

Recessive dwarfism:

A recessive type of achondroplasia has been described which is referred to as the "Telemark" type (110). The heterozygous Telemark cattle appear normal. The monsters were born alive after full term gestation and died within a few days from asphyxia (180). A known heterozygous Telemark bull was mated with eight Dexter cows. During the period, 1926 to 1931, 24 calves and a mummy were produced which included five long-legged calves, eleven typical Dexter calves, and eight which were not classified--probably long-legged--but no monster was produced. Neither the hypothesis of identical genes for both conditions nor the hypothesis of multiple allelomorphs could be supported because no monsters were produced in the above cross. The probable explanation was that these two lethals were quite independent, and that each breed carried the normal factor corresponding to the lethal of the other breed.

"Bulldog" calves have been reported in the African Uganda cattle (32). The Uganda breed of cattle is supposed to have originated from a cross of the long-horned Ankole breed and Easter Province animals, which are typical Zebus of small size. The "bulldog" condition in the Uganda breed was not uncommon, but they were never recorded by the natives of Uganda because they considered this condition to be an omen to the herd and the owner. People refused to look at the monsters. If a woman looked at one, it was believed she would produce a child with a similar condition.

Three achondroplasic calves have been described in the Jaroslav breed in Russia (138). All three dwarfs resulted from the mating of a champion cow "Zolataja" to her son, grandson, and half-brother, respectively. The dwarfs had deformed lower jaws and shortened legs. One of these dwarfs could not eat grass and hay, but the other two, although they had shortened lower jaws, could eat normally. They did not live long. It was felt that this was a milder form of achondroplasia than other types which had been reported at that time. It was concluded that the sires were heterozygous for the monstrosity.

"Bulldog" calves were also reported in the Guernsey, Jersey and Ayrshire breeds, all apparently caused by the homozygous condition of a recessive gene (24). Dwarf cattle are also reported among the original Spanish cattle in Puerto Rico (4). A new sublethal type of achondroplasia was brought to light as a result of the inbreeding of Jersey cattle at California (89). It was recessive in nature, but more variable in its phenotypic expression than the Telemark type. The greatest modifications seemed to occur in the development of the bones of the skull and jaw. Defective calves could be identified at birth by a short, broad head, and a prominent forehead. Cleft palate might be observed in severe cases and the maxilla was sometimes shortened. The gene involved "has little, if any, effect on leg length". The dwarfs died after birth, although one achondroplastic female lived to 14 months of age.

Jersey "bulldog" calves that have notched ears have been described (226). In addition, they have shortened maxillae, bulging eyes, short, gnarled legs, no tails, and were hermaphrodites. They were full term and born alive. Jersey "bulldog" cattle are described as having skulls broader and shorter than normal (12). The nasal bone is particularly short and broad, and the poll is wider between the cores. The orbits are large and upper jaw short. The animals apparently have impaired vision.

"Stumpy", a recessive achondroplasia in Shorthorns, has been described (6). This type of dwarfism was discovered following a line-breeding program in a purebred Shorthorn herd in Central Nebraska. The dwarf or "stumpy" calves had three common characteristics:

1. They had curly coats and smaller switches. By these characteristics the "stumpy" individuals could be detected at birth.

2. An achondroplastic condition, more marked in the forelegs than in the hindlegs. The knees were enlarged. The cannon bones were twisted. The body and head seemed to be normal in size.

3. Metabolic disturbances were present in all "stumpy" calves. Most of these animals were thin. These dwarfs live and reproduce, and, although the condition is not lethal, it is a serious economic loss to breeders. No post-mortem examinations were made and the endocrine glands were not studied. No measurements of the animals were taken.

Between 1937 and 1946, a total of 562 calves were born in the inbreeding program. Among these were 26 dwarfs. The incidence of dwarfs in the herd for that period was, therefore, 4.6 percent. All of the dwarfs had a common ancestor in which the mutation might have occurred. From an analysis of the pedigrees, it was concluded that the "stumpy" syndrome was caused by a single autosomal recessive gene.

West African Shorthorn cattle have been described that are dwarfed in stature, humpless, and do not resemble Zebu in any characteristic. A full-grown bull will weigh 350 pounds and measure about 36 inches to the top of the withers. They appear to breed true genetically since they do not change even under optimum environmental conditions (114).

There is a reported occurrence of a "Dexter monster" which was dropped by a Jersey-Holstein crossbred cow that had been mated to a Holstein bull (54). The monster had no hard palate and no hypophysis. There was only one parathyroid. The thyroid gland was small while the thymus gland was large and active. The skull and skin were abnormally thick and the brain microcephalic.

An achondroplastic type found in Swedish Red and White cattle appears to be similar to dwarfs found in some of the British breeds (117):

1. Head short and broad with moderately bulging forehead
2. Upper jaw noticeably shorter than lower jaw
3. Legs comparatively short, particularly below knee and hock; the calves stand on the tips of their toes, and on the hind-legs the toes in most cases turned under--the condition improved so that the calves could walk fairly well in a week or two
4. Gestation length normal
5. Excessive amniotic fluid noted in many cases
6. Bull calves showed more pronounced symptoms than heifer calves.

The indications are that the heterozygotes are somewhat achondroplastic.

A proportionate type of dwarfism is known in Jersey cows (153). They tend to be smaller at birth but weights and measurements lie within normal range so dwarf animals cannot be identified by differences in general appearance early in life. At maturity they are distinctly smaller than normal cattle. It is due to a single autosomal recessive.

Akroteriasis congenita (amputated) was reported in the Swedish breed of Holstein-Friesian cattle (247, 248). In the homozygous condition it was characterized by an extremely reduced mandible and maxilla, fore-legs amputated at the elbows, hindlegs amputated at the hock joint, and a pronounced hydrocephalus. The calves died at full-term. Among 115 calves produced by the mating of heterozygous bulls to their daughters, 102 were normal, 13 were amputated, which fits the expected ratio of 101:14 according to the hypothesis of a single recessive gene. The gene was probably imported from Germany and was widely spread in Sweden.

A gene for short spine when in the homozygous state caused an extremely short neck, thorax, and tail, in the Oplandske mountain breed of cattle in Norway (164). The calves died after full term. In some, atresia ani was present. This condition was attributed to a single recessive sub-lethal gene.

An undersized Hereford steer has been described as having a "general dwarf-like appearance, short and irregularly curved legs, abnormally large joints, short and thickened face, and a nervous disposition." It was fed and treated for one year like the show cattle and during this period it improved a little. The calf was sired by a purebred Hereford bull out of a good grade Hereford cow. Upon post-mortem

examination, they found that the epiphyses of the long bones were enlarged and irregularly curved. The thyroid gland was about one-fifth of the normal size. The parathyroids were correspondingly small, and the pituitary was only about 50 percent of the normal size. It was suggested that this condition might be due to the underdeveloped thyroid and pituitary (42).

A recessive type of dwarfism present in Angus has been reported (7). Dwarfs were always distinguishable at birth. At varying ages from birth to two or three months, they usually exhibited exceptionally compact, low-set, thick bodies, with short, wide head. They usually did not gain or fatten normally and after a few months did not show the same thickness and degree of finish as they had at an earlier age. The head also appeared relatively longer and narrower than at an earlier age. Bull and heifer dwarf calves were produced in approximately equal numbers. The condition is due to a single autosomal recessive gene.

The Hereford dwarf has probably received the most attention recently (118). Its occurrence is quite frequent. The dwarfs were thick and blocky at birth, and most of them caused calving difficulties because of their characteristic greater width of body. This was especially noticeable when the mother of a dwarf was a heifer. Sometimes death occurred due to dystocia. Most of the dwarfs died before they were one year of age. The symptoms of dwarfism became increasingly pronounced with age due to retarded growth. Most of them were chronic bloaters and some died of that cause. Slightly bulging foreheads were common, but this alteration was not always extreme and might not be present. It was reported that the lateral ventricles of the brains of dwarfs contained more than the normal amount of fluid. In a two-year-old dwarf bull, spermatogenesis was present. No defect of the endocrine glands was found in the two dwarfs examined histologically (118).

A more comprehensive study was made of dwarfs in the Hereford, Angus, and Shorthorn breeds (92). All of the dwarfs had thick, heavy, labored breathing as if they had some respiratory trouble. The mandible, with some malocclusion of the incisors with the dental pad, was longer than the maxilla. The dwarfs were low set, compact, blocky, short of neck, wide through the body, and had a broad, short face. The shortening of the long bones and the bulging of the foreheads were common characteristics of these dwarfs within the Hereford, Aberdeen Angus and Shorthorn breeds. At two to four months of age, the dwarfs appeared to be stunted and potbellied and they were able to breathe with difficulty. Physiological studies indicated that the dwarfs have a deficiency of the thyrotropic hormone. It was suggested that probably more than one type of dwarfism was involved within each breed of the Hereford, Angus, and Shorthorns. Hereford and Angus dwarfs have been shown to have pituitary, thyroid, adrenals, ovaries and testicles almost normal (136).

Calves from dwarf X dwarf matings are phenotypically similar to dwarfs produced by heterozygous parents (174). Experimental results indicate that nutrition cannot be associated with this type of dwarfism.

A study has been made of head characteristics in an attempt to identify heterozygotes (93). A study of the median profile of homozygous and heterozygous horned Hereford bulls shows that the heterozygotes are generally characterized by a slight bulging in the midforehead region. This permits an accurate differentiation of the two genotypes which are otherwise apparently phenotypically normal. This type of dwarfism is

due to an autosomal recessive gene (93, 118, 174). It also appears that the incidence is increasing since breeders have definitely, though unconsciously, favored the heterozygote especially in the selection of sires (93). It has also been observed that dwarfs are not likely to be encountered except in the progeny of short-legged, brachycephalic animals (110). (Author's note: P. W. Gregory, in a personal communication, has pointed out exceptions to this generalization).

A congenital deformity that is non-hereditary has been described (98). Osseus development of the head in different affected animals is not consistent; there exists an achondroplastic-like condition with shortened head length, usually accompanied by undershot jaw, and the long bones of the fore and hind limbs are markedly shortened. The condition is not hereditary, but the specific deficiency or deficiencies involved have not been ascertained.

"Short spine", reported in the Norway Oplondske breed, and "amputated", in the Holstein-Friesians, have been compared (164). The affected Oplondske calves are full term, but are stillborn or die immediately after birth. The legs are normal in length, but the entire spinal column is shortened. This shortening is due to aplasia or reduction in size with irregular fusion and amalgamation of adjacent vertebral rudiments during development. It is due to a single recessive gene.

Hydrocephalus:

For any marked enlargement of the head to occur, the increased intracranial pressure must be present early in developmental life. Hydrocephalus is readily produced in mammalian forms and may follow either ventricular block or a diffuse meningeal block.

In a cross of a Durham bull on a Jersey-Hereford cow, a hydrocephalic calf was born. The hydrocephalus resulted from a congenital malgrowth in the diencephalon with a constriction of the third ventricle to a very narrow canal (104).

In Holstein hydrocephalic calves, the internal hydrocephalus was accompanied by a marked papilledema. The lateral ventricles were greatly distended so that only a thin layer of cerebral tissue remained between the cavity of the ventricles and the cranial bones. Both the humeri and the femurs of these animals showed marked malformation. The shafts of these bones were considerably shortened but larger in diameter than the normal (39).

"Asymmetry" (wry face) and "jumpy" (muscular incoordination) were found associated with hydrocephalus. The hydrocephalus appears to be due to a simple recessive. Recessive hydrocephalus has been reported in the Marche breed (76). In many cases, hydrocephalus was accompanied by malformation of the limbs. Recessive hydrocephalus was also reported in Jersey cattle (65). In a report covering the general consideration of hydrocephalus in calves, it was stated that congenital internal hydrocephalus of the newborn may well account for a considerable number of unexplained losses in calves during the first few weeks post partum. It is a condition which is apparently not too uncommon and which may not be readily recognized at birth or shortly thereafter (20).

Hydrocephalus is apparently produced by a failure of the drainage mechanism of the ventricles of the brain. The cerebrospinal fluid secreted by

the ependymal cells of the choroid plexus is retained and accumulates within the ventricles. This excess fluid compresses the soft tissues of the brain against the bones of the cranium, resulting in doming of the calvarium, neurologic symptoms, and death. The author considers the possibility that hydrocephalus was due to a vitamin A deficiency in the dam. Vitamin A deficiency has been studied in this regard (166).

Presence of papilledema is usually considered prima facie evidence of an elevated cerebrospinal fluid pressure:

a. A deficiency of vitamin A in the ration of the young bovine produces an increased cerebrospinal fluid pressure.

b. The increase in cerebrospinal fluid pressure is accompanied by papilledema, nyctalopia, syncope, and incoordination.

c. On return to normal diet, the cerebrospinal pressure slowly returns to near normal, while the quoted disturbances disappear.

In one animal, the ventricles of the brain were distended, being three to four times the normal size.

A hydrocephalic condition has been reported in the Duroc-Jersey breed of swine (18). It was an external type of hydrocephalus, the fluid being found in the subarachnoid spaces. This character was found associated with the dilution of coat color and a short tail, or no tail. The body size of the hydrocephalic pig was reduced. It was a lethal character for swine. The young pigs were either stillborn or died shortly after birth. This condition is due to a simple recessive gene.

Related characters in cattle:

A spastic syndrome has been reported in cattle (188). It is probably a disease of the central nervous system, usually affecting older cattle. It is characterized by spastic contraction of muscles of one or both hind legs, back, and eventually the entire body. The cramps last from several seconds to a few minutes or longer and then cease suddenly, only to be repeated upon the proper stimulus. The attacks are mild for several years before a severe attack occurs. Symptoms are most evident when the animal first gets up or is startled, and are absent when the animal is recumbent. The animals appear to be less affected when on pasture, exercised moderately, and kept isolated and quiet. This characteristic has been observed in Holstein, Guernsey, Ayrshire, crossbred Brahman, and Shorthorn. It has definite familial occurrence but the exact hereditary nature has not been determined.

Congenital ataxia has been described in Jersey calves (195):

1. Some calves showed symptoms at birth, others not before two or three weeks
2. Calves would fall down, walked like a ballet dancer
3. Calves had good appetites.
4. Calves well formed and appeared bright and alert
5. Due to anomaly of cerebellum and mid-brain--consisted of lack of development of nerve cells, axon cylinders, myelin sheaths and oligodendroglia in these regions
6. Apparently due to a simple recessive

Hereditary congenital lethal spasms are also known in Jersey cattle (90). The calves appear robust and healthy except for certain convulsive movements. The calf could stand but never did so voluntarily. The condition is due to a simple recessive. A check list of hereditary and familial diseases of the central nervous system in domestic animals has been compiled (194). Some of the selected examples are:

	BREED	CHARACTER	INHERITANCE
1.	Brown Swiss	Epilepsy	Dominant
2.	Danish Red	Congenital posterior paralysis	Recessive
3.	Hereford	Ataxia, cerebellar hypoplasia	Not reported
4.	Holstein-Friesian	Spastic paresis	Recessive
5.	Swiss Spotted	Spastic paresis	Recessive
6.	Holstein-Friesian	Spasms	Recessive
7.	Jersey	Spasms	Recessive
8.	Norwegian Red Poll	Paralysis, spasms of neck	Recessive
9.	Simmental	Tremor of fore limbs	Not reported

A deformity of the lower jaw has been reported in Milking Shorthorns (3). The jaw is only half normal length. It is due to a recessive gene. A malocclusion due to mandibular prognathism is also reported due to a dominant gene with reduced penetrance (219).

Sheep and goats:

Dwarf lambs were produced in a strain of Southdown sheep (19). They had short legs, thick shoulders and bulging foreheads. The dwarfs gained in weight for a short period of time and became "puffy" fat in appearance. They died within a few weeks after birth. Some of them had short under jaws. Therapy with desiccated thyroid appeared to be beneficial. It is due to a simple recessive.

The ancon mutation in sheep represents the earliest recorded mutant among domestic animals. It is, therefore, interesting to study (125). In 1791, the first ancon lamb was born in Dover, Massachusetts. The owner, Seth Wite, Jr., accepting the advice of his neighbors, killed the ram heading his flock of fifteen ewes and used the young ancon for breeding. A few more lambs distinguished by the same peculiarities were dropped in his flock. Thus, a new variety of sheep came into the world. It was named the "Otter" breed after its real or imaginary resemblance to the otter in shortness of its legs and length of its back.

A Boston surgeon, Dr. George Chayne Shattuck, dissected one of these sheep and reported that it had loose articulations and small bones. He noted especially the crookedness of its forelegs, which caused them to appear like elbows when the animal walked. He called them "ancon" from the Greek word which signifies "elbow".

Hejaz goats resembled the goats of prehistoric ages. They were of uniform type with harmonious proportionate growth. They had bulging foreheads. The auricula was occasionally atrophied, and only the scantiest vestige remained. This trait was called "earless" as they had ears half as large as those of normal goats. In the F_2 generation, this character segregated in the proportion of 25 percent homozygous earless, 50 percent heterozygous short-ears, and 25 percent homozygous normal ears (67).

The study of the characteristics revealed that the Hejaz goat was considerably smaller in size than goats of neighboring states and that it was an established breed.

It is stated that the small structure of the Hejaz goat was due to pituitary hypoplasia. It is suggested that this dwarf breed had arisen due to natural selection which was helped by artificial selection and inbreeding. Poor environmental conditions, especially scarcity of food, promoted the evolution of a small, hardy type of goat. The Hejaz goats interbred to such a degree that inbreeding helped to increase the rate of combination of mutant genes governing the pituitary hypoplasia. This system of breeding, without the introduction of any outside blood, explained the uniformity of the Hejaz breed.

A careful study has been made of the skeleton of the African dwarf goat (36). In one-year-old goats, the epiphyseal lines in the distal end of the humerus and the proximal end of the radius have disappeared whereas they are still present in normal goats of the same age. These bones do not have the characteristics of chondrodystrophy as in creeper fowl and ancon sheep. Reproductive functions appear normal. There is no indication of dysfunction of thyroid or pituitary.

TABLE 10.--Measurements (in mm) and percentage retardation of skull of the African dwarf goat (36).

	Newborn			One Year Old		
	Normal	Dwarf	Percent Retardation	Normal	Dwarf	Percent Retardation
Total length of skull	114.7	108.1	5.7	203.4	163.5	19.6
Interfacial turbosity distance	43.1	39.7	7.9	64.8	57.7	11.
Cranial width	56.8	50.6	10.9	67.2	58.	13.7
Skull height	56.6	51.1	9.7	93.6	78.	16.6
Mandibular length	85.4	76.6	10.3	154.8	114.	26.4
Mandibular height	42.7	41.	4.	88.4	70.	20.2

TABLE 11.--Length (in mm) and percentage retardation of leg bones of the African dwarf goat (36).

	Newborn			One Year Old		
	Normal	Dwarf	Percent Retardation	Normal	Dwarf	Percent Retardation
Scapula	72.1	66.	8.5	114.6	103.8	28.2
Humerus	94.9	78.7	17.1	161.9	112.1	30.8
Radius - Ulna	117.9	94.6	19.8	202.5	139.2	31.3
Metacarpus	75.4	58.4	22.6	111.8	78.2	30.1
Phalanx I	25.8	20.6	20.2	40.6	30.1	25.9
Phalanx II	19.	15.3	19.5	28.3	21.7	23.3
Femur	100.6	85.5	15.	188.2	127.2	32.4
Tibia	116.	98.6	15.	217.	148.	31.8
Metatarsus	76.	60.2	20.8	116.7	81.3	30.3
Phalanx I	26.5	20.8	21.5	3.9	29.7	23.9
Phalanx II	19.	15.1	20.5	31.8	21.3	33.

EXPERIMENTAL ENDOCRINE DISTURBANCE

In a thyroidectomy, care must be taken to assure complete removal. If, after surgical treatment, only very small remnants of thyroid gland tissue are left functioning, these remnants (under conditioning and perhaps stimulation) preserve the typical properties of the total gland in hyperthyroidism (17).

The principal effect of thyroidectomy at birth in the rat was manifested as a marked retardation in the growth and maturation of the animal. The rat thyroidectomized at birth had the following characteristics (201):

1. Exceedingly slow but continuous increase in body weight and size of skeleton

2. Delay in appearance of secondary ossification centers

3. Reduction in oxygen consumption

4. Marked retardation in the transformation of hair from the infant to the adult type

5. Delay in eruption of teeth

6. No apparent increase in susceptibility to intestinal disorders and infection

7. Hearty appetite

8. No symptoms of tetany

9. Eyeball and brain practically equal in absolute weight to those of the normal rat, being greater in proportion, therefore, to body weight; intestines likewise being proportionally larger in thyroidless rats

There was a tendency for excessive accumulation of gas in the intestines. This accumulation of gas was correlated with the occurrence of the protuberant abdomen.

In attempts to produce experimental thyroid hyperplasia, it was found that adult rats kept under hygienic conditions and fed a high protein diet developed hyperplasia of the thyroid gland (31). Rats kept under unhygienic conditions developed hyperplasia of the thyroid if given a standard diet of bread and milk.

Hereditary dwarf mice of the silver strain and hypophysectomized rats were found to be similar conditions (209). In both cases, growth was either absent or much below normal. The thyroids and adrenals were markedly imperfect. Implants with fresh anterior pituitary restored both of these conditions to nearly normal. However, an outstanding difference between the hereditary dwarfs and hypophysectomized rats was the degree of development of their reproductive systems. In hereditary dwarfs, the testes and the motility of the sperm were not greatly different from normal. In hypophysectomized rats, the testes became flabby, the sperm did not develop, and the seminal vesicles and other glands became greatly reduced in size. The ovaries of hypophysectomized rats were less active than those of hereditary dwarfs. The uteri of dwarfs were infantile, whereas the uteri of hypophysectomized rats were thread-like. This suggested that the pituitary growth hormone of the dwarf was suppressed without a corresponding suppression of the gonad-stimulating hormone. There was a high concentration of the gonad-stimulating hormone in the pituitaries of the hereditary dwarfs, whereas workers failed to detect the presence of growth hormones.

Many biological variants have been produced among the descendents of mice which had been injected subcutaneously with methylcholanthrene for many generations (224). Dwarfs have been produced which are smaller than normal at birth, and generally die before weaning. The condition is due to a simple recessive.

Eighty-seven domestic rabbits were thyroidectomized at 13 to 21 days of age (107). Thyroidectomy retarded development of the face and cranial base. In breadth, the skull showed disproportionate retardation in the face and forehead. The development of the face showed a retardation comparable to that of the skull. Verticle growth of the mandible was also significantly retarded, indicating a generally underdeveloped jaw. These effects were greater in the female. The bone of the upper and lower jaw was markedly porous. Cranial bone vaults (parietals and frontals) were thinner than normal.

A comparison of control and thyroidectomized skulls showed that physiological insufficiency of thyroid secretion was manifested within six days. The skull weighed less and there was difference in over-all length, most

of which was due to the shortening of the face in the region anterior to the premolar teeth. Superior facial breadth was also distinctly narrowed. The animals were identical in all measurements except those of the face. Of the two regions most affected by thyroidectomy, face and skull base, the face was affected first. The shortness of the diastema, so marked in adults, was already present.

In only partly excised thyroids of rabbits, the hormone exhaustion was promoted by pregnancy (10). Calculus in the bladder was associated with degenerative changes in the kidneys of thyroidectomized animals.

Extirpation of the thyroid gland of young pups resulted in retardation of growth through cell metabolic disturbances which did not affect all parts of the body alike (60). There was retardation of the ossification of cartilage bone and delayed ankylosis of the sutures of the skull bones. There was no effect on membrane bone development. This retardation of growth of skull bones mechanically altered the skull shape with resulting brachycephaly, depressed root of the nose, shortened superior and inferior maxillary bones and hypochondroplasia (59).

Hypophysectomized dogs are more susceptible to disease (47). Distemper and pneumonia are the usual causes of death. Other characteristic symptoms are:

1. Low mentality
2. Retain soft puppy hair, first denture, and infantile sexual apparatus
3. Skeletal growth stops almost immediately after hypophysectomy
4. Closure of epiphyseal lines delayed to 19 months--they normally close between the 7th and 9th month
5. Thyroids, adrenals, sex glands, and pancreas exhibit cessation of growth or actual recession in size after operation

The symptoms associated with hypophysectomy of growing chicks are listed as follows (171):

1. Very lethargic
2. BMR decreased 30-50 percent
3. Gait clumsy
4. No sex interest
5. Become mute
6. Up to 260 days following operation they deposit and contain five times as much fat as controls
7. Pronounced hypertrophy of gall bladder
8. Death attributed to a disturbance of the carbohydrate metabolism
9. Thyroids respond in 10 to 20 days, become very small
10. Adrenals undergo almost complete degeneration
11. Feather growth slow

Behavioral, physical growth and metabolic features were investigated over a four-month period in two infant Rhesus monkeys whose thyroids were ablated in the neonatal period and over a similar period in two others whose thyroids were ablated at four and five months, respectively (179).

I^{131} in amounts necessary to produce thyroid ablation caused neither significant change in the formed elements of blood nor hypoparathyroidism. Characteristic behavioral and physical changes similar to those common to

the human athyroid appeared 15 to 20 days following thyroid ablation and were marked by 40 to 45 days.

1. Macroglossia
2. Generalized myxedema
3. Labored breathing
4. Showed sluggish motor activity
5. Generally, lassitude and somnolence replaced alert inquisitiveness.
6. Marked deficit in over-all growth
7. Assumed sitting or crouched position
8. Hair coarse, irregular, and dull
9. Delayed teeth eruption
10. Enlargement of palatglossal and palatopharyngeal arches
11. Abdomen doughy and protuberant

Coincident to the changes, voluntary caloric intake dropped 50 percent and growth stopped. Nitrogen, calcium, and phosphorus retention was greatly reduced from normal and fluctuated with the varying degree of myxedema. Similarly, urinary creatine and creatinine excretion averaged 50 percent of normal.

The thyroidectomized bovine shows characteristic changes 30-60 days after thyroidectomy (213).

1. Diminished appetite
2. Decreased activity
3. Increased susceptibility to low temperatures
4. Enlargement of the paunch
5. Hair becomes progressively dry and brittle
6. Skin becomes thick and dry
7. Animals seem to have difficulty raising their feet and shuffle along
8. Decreased pulse rate
9. Subnormal temperature

A heifer was thyroidectomized on the 46th day of her first gestation period. Growth was static for about 20 weeks following thyroidectomy. However, coincident with the last 10 weeks of the gestation period, a sudden resumption of height and body weight gain occurred. Following parturition, growth again became static and little change was noted until the latter part of the subsequent gestation period when growth was resumed.

It appears that the thyroid deficiency of the mother was remedied, partially at least, either by diffusion of the thyroid hormone from the fetus into the maternal circulation or by some undefined factor related to the pregnant state.

Thyroidectomy caused complete inhibition of libido but no apparent effect on spermatogenesis. Thyroidectomized cows failed to manifest normal physical signs of estrus but could be impregnated and calve (213, 184).

A study was made based upon the skulls and skeletons of five pairs of twin sheep, one of each pair being thyroidectomized early in life (231).

The general results but not necessarily the specific or direct effects of thyroidectomy are:

a. Deficient growth and modelling of the epiphyses themselves
b. Defective development of age characteristics on both epiphysis and adjacent shaft

c. Diminished velocity of growth of shaft--there is no modification of bone texture, weight, thickness, or modelling of shaft and no prolongation of the growth period to compensate for diminished velocity

The locus of damage to both growth and maturation patterns is definitely and solely the diaphyso-epiphyseal plane. Thus, body framework is affected but viscera and brain largely escape mutilation both in size and structure.

Obvious pathological changes in the diaphyso-epiphyseal plane are not evident until the animal is two years old or more. The pathological features are:

a. Irregular exuberances on the shaft and resembling ossified "proud flesh"
b. Inturned, clawed, trachoma-like epiphyseal margins
c. A small, poorly modelled, ill-fitting epiphysis scarcely covering the shaft end

In the skull, the disturbance of developmental growth is most marked in the pre-maxilla and maxilla but also affects other parts of the face. Tooth development is slowed down, eruption of permanent teeth (except first molar) is delayed. Teeth are neither reduced in size nor mutilated. The growth of the mandible, uncompensated by similar growth in the upper jaw, causes protrusion of the incisors beyond the upper lip.

Modification of skull pattern is to be sought in local defect of growth rather than in general measurements or in cephalic index.

In another study with thyroidectomized sheep, skull differences were carefully noted (135). Dwarfed skulls were foreshortened and disproportionately wide. The nasal and frontal bones were more retarded in growth than the parietal and occipital. Delayed dentition was observed. Ankylosis of the basisphenoid and basioccipital was very slow in comparison to normal.

Cephalic index: Controls 49.8 - 51.1
Thyroidectomized 51.8 - 53.4

Goats were thyroidectomized when 5 to 24 days old (185). By the end of the second week the kids acquired a dull, sleepy appearance, usually stood in a relaxed position, and had a diminished appetite. By the end of the second month there was a shortening and thickening of the body and an enlargement of the paunch. Growth of the muzzle and jaw bones lagged behind that of the upper portions of the head with the result that an extremely dish-faced appearance developed.

A summary of the effects of thyroidectomy on the skull has been presented (230). It was reported that a technique dependent upon dimensional measurement does not give adequate realization of the resultant disturbance, first, because we are dealing with growth, which is not static but progressive, and, secondly, because the growth disturbances are not uniform. We do not know how diet may have modified the aberrant course of growth.

There is no defect in tooth formation, although there is a delay in tooth eruption. Dental age as measured by tooth eruption is a good measure of thyroid disturbance. Defective growth in the lower frontal-lachryional-molar area means that the upper jaw is never thrust downward to the degree

seen in normal growth. The net result is a cramped, ill-developed snout, a "juvenile" steep forehead and an up-curving of the hard palate.

There is no defect in the growth of the brain-case proper or of the orbit and very little in the hafting zone (deeper orbit and palate-sterygoid). The occipital area undergoes some superficial defect secondary to the facial deformity. There is no demonstrable defect in mandibular growth. Defective growth does not follow any rigid pattern or time schedule.

Another summary reports a prepotent factor in the determination of skull shape (59). Normal growth tendencies in the basal bones of the skull are in the direction of increased length relative to width as age advances. Brachycephaly is characteristic for young animals and as age advances the skulls become more and more dolicocephalic. The picture presented by these basal bones of cretin skulls is then in the direction of retarded growth. This is probably the primary factor, but that it is not the only one would seem to be shown by the fact that when cretin and normal animals of approximately the same size are compared, the basal bones of the former are not only as broad relatively, but may be actually broader.

A second fact which seems to indicate a disproportionate growth following thyroidectomy is found in the forward shift of the nasian and posterior parts of the cranium. It would seem that cretins are not merely small animals in respect to shape and size of skull but the shift in relations is determined wholly by normal growth tendencies being distorted by a disturbed development of the basal cartilage bones. Restricted growth in these bones, together with a similar disturbed growth in the ethinoid bones which form a rather inflexible base, cramps cranial and brain growth in the anterior-posterior direction. In these the normal potentialities seem to be almost undisturbed as is indicated by the general development of the cranial vault. This cramping results in both lateral and posterior expansion of the cranium, the direction of least resistance, to accommodate the relatively more rapidly developing brain.

Other characteristics commonly associated with brachycephaly are shortened inferior and superior maxillary bones, and changes in shape and saddling of the nose. These would seem to be the result of a single cause, hypothyroidism.

THERAPY

Therapy is an important consideration in an investigation of bovine dwarfism. If successful procedures for therapy can be determined, it will permit investigators to grow out genetic dwarfs to permit their use in breeding tests. Because of the small size and general poor health of the dwarfs, they are at present difficult to use in such tests. Secondly, if a satisfactory therapeutic material is determined, it is actually evidence of a deficiency of that particular substance in the affected animal.

In cases of clinically typical cretinism in humans, thyroid therapy has been generally successful. Doses of 1 to 15 grains of desiccated thyroid administered to cretinous infants resulted in marked physical improvement in all cases, with development of a normal appearance and acceleration in physical growth, particularly in the length of legs (75).

Thyroid therapy can promote a normal condition in the newborn baby with clinical cretinism (112). In one case, tests showed thyroxine present in

the plasma and gland that would indicate hyperthyroidism, although the clinical symptoms indicated hypothyroidism. Thyroid therapy proved successful (106).

Withdrawal of the treatment from these children again produced the characteristic deficiency symptoms and retarded growth (198). In adult hypothyroidism, replacement therapy with thyroid hormone usually results in complete cure. The preparation of choice is desiccated thyroid. The initial dose should be small because many myxedematous patients react to a rapid increase in metabolism with tachycardia, some with nervousness and even psychosis (175).

The authors suggest a daily dose of ½ grain. If this proves ineffective, increase the dose in steps of ½ grain at three-week intervals (81, 175, 25).

A general guide has been prepared that shows the characteristics that can be expected to change during therapy in humans (229), Table 12.

Cretins, if treated, are not predestined to a fixed low mental age. A small proportion of them develop normally. However, even with treatment, most of the children remain severely retarded, having an intelligence quotient below 70 (27). In adults, treatment of myxedema in the last stages is ineffective (130). Thyroid therapy has proved successful in curing sterility (129) and treating hay fever and asthma (204).

There are cases of apparent hypothyroidism that show a marked sensitivity to oral thyroid medication. It has been reported that the administration of ACTH increases the tolerance to thyroid (216, 217). These investigators reported some clinical improvement with ACTH or cortisone alone (216). Normal growth was produced in 14 of 18 patients with 5cc of pituitary extract given intramuscularly two times a week, plus full tolerant dose of desiccated thyroid (196). This does seem odd since the presence of circulating thyroxine definitely interferes with the response of the thyroid to injected thyrotropic hormones (41).

TABLE 12.--Expected response to thyroid therapy in human hypothyroidism (229).

Change noted	Time after thyroid therapy started Ave. (weeks)	Range (weeks)
1. Body weight loss	2½	1½ - 7
2. Increased physical activity	3½	½ - 11
3. Drop in serum cholesterol	3½	1 - 6
4. Increased appetite	4	1 - 11
5. Loss of constipation	5½	1 - 11
6. Increased growth rate	8	3 - 16
7. Disappearance of skin dryness and coarseness	10	4 - 20
8. Loss of myxedematous appearance	11	6 - 20

The growth rate of rats completely thyroidectomized at birth was stimulated by a purified preparation of anterior pituitary growth hormone (200).

a. Body weight doubled in 22 days
b. Skeletal size increased at an accelerated rate
c. No acceleration was observed in the appearance of secondary ossification centers

Goats, thyroidectomized 5 to 24 days after birth, developed typical cretin symptoms. These animals were administered .03 gram to 1 gram of thyroprotein daily in a gelatine capsule. The oral administration of this artificial thyroprotein, produced by the iodination of skim milk proteins, arrested the development of cretinism and stimulated growth approaching that of normal (185).

Thyroid tissue from a twelve-week fetus was transplanted to the rectus muscle of a 64-year-old female with myxedema. Four weeks later no evidence of function was found with I^{131}(30).

Thyroxine, which promotes the growth of thyroidectomized animals, does not have this effect when administered to thyroidectomized-hypophysectomized animals (68).

When thyroid was administered to hypophysectomized animals, there was no stimulation of growth: when thyroid and anterior pituitary growth extracts were given concurrently, the growth response exceeded that obtained when pituitary extract was given alone (197).

In the hereditary pituitary dwarf mice, injection of anterior pituitary fractions caused a 30 percent gain in body weight in 30 days (9). Therapy for hypopituitarism is also listed as thyroid in conjunction with a high protein, high carbohydrate diet (132).

A method of assay for clinical study of thyrotropic substance has been presented (181). The increased height of the acinar epithelium of the guinea pig thyroid induced by thyrotropic substance may be found by direct micrometer measurements and the hyperplasia throughout the gland may be represented by a frequency curve derived from these measurements.

There apparently is agreement that nothing can be done for the Mongolian idiot (175).

DISCUSSION

Dominant achondroplasia has been reported in humans, cattle, poultry and small animals (74, 167). The possibility of two independent, complementary, dominant genes being involved has also been considered (103). In humans, there are examples of familial cretinism which do not seem to follow a single established hereditary pattern (133). Sporadic goiter, which is closely associated with familial cretinism, is apparently inherited as a single dominant (119) but is sex influenced in that more females are affected (119, 158). Some of the apparent discrepancies to this hereditary pattern appear to be due to the fact that this condition may lie latent in an individual living in a sheltered environment, but will develop under stress of anxiety or fear (182).

The Shorthorn, Angus and Hereford dwarfs which have appeared in increasing frequency during the past few years are genetically recessive in inheritance (6, 7, 92, 93, 118, 136, 174), although it has been suggested that more than one type of dwarfism is involved within each of these breeds (92, 93).

In such a trait as dwarfism, the gene cannot produce the trait without the cooperation of many other genes. A gene is one factor in a very complex chemical equation. Just as the introduction of the same compound into different chemical equations does not necessarily lead to the same modification of the result, so the effect of a given gene may differ according to the genetic equation into which it is introduced (9).

The lethality of factors is always an expression of their effect in a particular environment. Modifications of this effect both in a positive direction, with the result of lessening it, and in a negative direction, with the result of making it more deleterious, may result from changes in the environment; to this end, external means as well as genic modifiers may be effective. The dependence of the effect of lethal factors upon the external and internal environment is, of course, a feature of the action of genes in general, none of which produce their effects in vacuo but all of which are highly dependent for their expression on the rest of the total genotype as well as the environmental conditions in which they find themselves. If we speak of "lethal" factors, we must always keep in mind that such factors may lose their lethal character, or at least modify it, in an environment different from that in which it was found originally (79).

Among endocrine disorders causing dwarfism, hypothyroidism is probably the most common (242).

The thyroid is more concerned with the process of embryonal unfolding than of growth (95, 205, 225). Since the functions and characteristic relationships of thyroid and hypophysis are established simultaneously with histological differentiation of the glands, the function of endocrine glands during fetal life is insignificant only under optimal environmental conditions in which the fetal organism develops. As soon as deviation from the optimum occurs, the endocrine system can be mobilized as one of the most important regulators of vital functions in the organism (70, 225).

If the thyroid deficiency occurs during prenatal development, the symptoms of cretinism are manifest relatively early in the life of the individual. However, even within the same family, the age at onset of cretinism can vary from a few weeks of age to puberty (133). If the achondroplastic syndrome starts at an early period of intra-uterine life, the dystrophy may be so severe that the fetus dies (115).

It has been recognized that hypothyroidism may exist in utero, may develop in infancy, in childhood, or in adult life (155). Cretinism is often not noticeable until the sixth or seventh month (82, 206) or even the first few years of life (240). The thyroid defect is actually congenital, but may remain latent pending its manifestations through the impulse of some circumstance (150). A child may be born apparently normal and function normally until he is attacked by some acute infectious disease or other condition which affects the thyroid gland. It seems in these cases that during the acute attack there is a call for thyroid on the part of the

body which depletes the reserve and permits the manifestations of the deficiency (83). If thyroid deficiency does not occur until in later childhood, the individual will have attained such growth that he cannot be classified as a dwarf (240). The symptomatology, physical changes and other abnormalities characteristic of hypothyroidism depend upon the degree of thyroid deficiency and upon the age of the child when the disturbance commenced (82). Since the thyroid hormone plays a role in growth and maturation, the effect of a lack of it during the growth period will be different and more devastating than during a time of life when full maturity and growth have been attained (155). When severe thyroid deficiency has existed over a considerable span of time during the early years of growth, it gives rise to the classical clinical picture described as cretinism (240). The differentiation of complete cretinism, partial cretinism, infantile myxedema, and juvenile myxedema is hard to make (81). Hypothyroidism has a gradual and insidious onset and is affected by the maternal hormone absorbed in utero and sources of hormone in milk and food.

The diagnosis of a genetic predisposition to hypothyroidism in young animals is very important. There is ample evidence to indicate that genetic dwarfs in cattle may actually be normal at birth and even for a considerable period during their life. Studies of these animals has indicated a relative and progressive, rather than an absolute, insufficiency of the thyroid hormone.

Symptoms due to loss of thyrotropic function cannot always be readily extracted from the composite picture on a purely clinical basis (175). The thyrotropic hormone secreted by the anterior pituitary gland is essential for the normal anatomy and physiology of the thyroid. The interrelationship between the two glands is mutual in that the secretion of the thyroid hormone likewise influences the pituitary gland, at least in respect to its thyrotropic hormone. An excess of thyrotropic hormone suppresses the output of thyrotropic hormone from the pituitary, thereby resulting in a diminished activity of the thyroid gland itself (41).

Since clinical tests cannot be used as the sole criterion of hypofunction of the endocrine glands, general appearance of any of the syndrome characteristics must also be considered. All of these symptoms are not likely to be found in any one individual; however, they all have been identified as being associated with hypothyroidism:

1. Failure of bone formation in cartilage
2. Epiphyses unite late
3. Brachycephalic skull
4. Dish-faced
5. Prognathic lower jaw
6. Macroglossia
7. Delayed tooth eruption
8. Coarse, harsh, scanty hair
9. Skin dry and scaly
10. Prominent and bulky abdomen
11. Susceptible to low temperature
12. Slow, grunting respiration
13. Skin pallid and cold
14. Mentally dull, drowsy
15. Defective vision
16. Defective hearing
17. Constipated

18. Anemic
19. Lowered BMR
20. Hydrocephalus
21. Increased cerebrospinal fluid pressure
22. Lumbar lordosis
23. High serum cholesterol levels
24. Elevated serum protein values
25. Reproductive ability affected
26. Abnormally short long bones
27. Generalized myxedema
28. Enlargement of palatglossal and palatopharyngeal arches
29. Fatty deposits in posterior triangle of the neck

The clinical methods that can be used as an aid in diagnosis of hypothyroidism are also included.

1. Radioactive iodine:

Since iodine is an important constituent of the thyroid hormone, the determination of iodine content of the gland would appear to be a measure of the activity of the gland.

Thyroxine and diiodotyrosine are the only two compounds of iodine known to exist in the thyroid. About 30 percent is in the form of the hormone and about 70 percent as the iodinated tyrosine (97).

In individuals that are definitely cretins, there is often a distinct deficiency of I^{131}.

I^{131} in doses of 5 to 10 MC were used to measure quantitatively both iodine uptake in the thyroid gland and urinary excretion in 25 enthyroid children and in 5 cretins. Over a 96-hour period the thyroid of the normal children took up between 8.7 and 29.8 percent with the maximum between 24 and 96 hours. During 96 hours their urinary excretion ranged from 29.3 to 70.6 percent. Repeated tests showed I^{131} uptake in the cretins to be negligible. It was between 1 and 2 percent and it was not appreciably influenced by thyroid therapy. The untreated cretins excreted 73.5 to 92.4 percent of I^{131} within 96 hours, while the same cretins when treated excreted between 35.8 and 84.5 percent in the same length of time (183).

In athyreotic cretins, studies have shown no uptake of radioactive iodine in the thyroid region (216). However, conflicting results have also been reported. In individuals that had typical clinical symptoms of hypothyroidism, radioactive iodine studies showed normal content in plasma and gland. In fact, one case showed hyperthyroidism (106). Studies with I^{131} after subtotal thyroidectomy showed hyperthyroidism (17). It is postulated that after surgical treatment only very small remnants of thyroid gland tissue are left functioning and that these remnants (under conditioning and perhaps stimulation) preserve the typical properties of the total gland in hyperthyroidism. An essential feature of these glands is the rapid turnover-rate of iodine with only a slight storage of organically bound iodine. In a rather complete report of radioactive studies in non-endemic cretinism it was determined that the amount of protein-bound iodine in the plasma 48 hours after the administration of radioactive iodine gives more valuable information about thyroid function than does either the uptake of iodine by the thyroid gland or its excretion by the kidneys (152). These investigators conclude that the thyroid

uptake and plasma content of radioactive protein-bound iodine in non-endemic cretinism add to the anomalous results reported in other investigations of thyroid disorders by similar isotope techniques. They emphasize how important it is that no laboratory test should take precedence over clinical assessment of the patient. Most of the amounts of iodine taken up by the thyroid glands and some of the amounts of protein-bound iodine found in the plasma in these cases suggested hyperthyroidism and might readily, without reference to the clinical picture, have been interpreted as indicating thyrotoxicosis. The amounts of iodine excreted in the urine were most consistent with the clinical stage.

The results of these investigations confirm other reports that the thyroid glands of cretins with non-endemic goiter are hyperactive and accumulate radioactive iodine ministered orally more rapidly and to a greater degree than normal (152). These investigations indicate that non-endemic goitrous cretinism may be caused by an inability of the thyroid gland to complete the synthesis of the thyroid hormone.

2. Blood cholesterol level:

Cholesterol, a sterol (complex monohydroxy alcohol), is present in all animal cells and is particularly abundant in nervous tissue. In the erythrocytes, most of the cholesterol is in the free state. In the plasma, some 20 to 40 percent is in the free state and the rest in the form of an ester (97). Blood cholesterol determinations are not particularly difficult.

High figures for cholesterol are found in hypothyroidism, such figures being roughly in inverse ratio to the basal metabolic rate, a low metabolic rate indicating relatively marked hypercholesterolemia. This relationship is considered by many investigators as a good index of the degree of hypothyroidism and is reported to correlate well with BMR (81, 82, 108). Since cholesterol levels are affected by the amount of circulating thyroxine, there must be considerable care used in the interpretation of findings. In a study of 70 patients with thyroid disturbance, the following points were noted (148):

a. Hyperthyroid conditions tend to diminish the level of the cholesterol in the blood. The lowest values are found in extremely toxic patients. There is, however, no constant definite correlation between the cholesterol value and BMR.

b. True myxedema is accompanied by a markedly elevated blood cholesterol. Low metabolic rates, however, without clinical evidence of myxedema, are accompanied by normal cholesterol values.

c. Cholesterol values are a definite help in estimating the gravity of hyperthyroidism.

d. Cholesterol values are important aids in diagnosis and prognosis and in estimation of response to treatment in patients with hypothyroidism.

If the thyroid disturbance is due to loss of thyrotropic function, serum cholesterol values are usually not proportionately elevated as is the case in "primary" hypothyroidism (175). Hypercholesterolemia, when not explainable on any other basis, may be considered as possibly of thyroid

origin and is a rational indication for thyroid administration. The findings of hyperholesterolemia, in the absence of its few other common causes, point more specifically to thyroid deficiency than do the findings of a low metabolic rate (108).

3. Roentgen studies:

In general, these studies indicate no progressive development of the bony changes in hypothyroidism. The metaphyses present a broad appearance with definite thickening, premature ossification, and limitation of growth. The epiphyses are slow to appear, irregular, and moth-eaten. The interarticular spaces are usually increased due to the small and poorly developed epiphyses. The kyphosis at the base of the skull is due to premature ossification (115).

Radiographic changes usually found in the spine are fragmentation and wedging of the bodies of the vertebrae. These may occur in any or all sections of the vertebral column. Detailed studies have been reported in humans (69, 82, 168, 189, 214, 240, 241), but no similar results are reported for animals.

4. Low body temperature (145)

5. Chronic hypoglycemia (217)

6. Eosinophilia (168)

7. In individuals that show cretin symptoms at birth, pathological changes in the thyroid gland are characterized by an extensive chronic productive inflammatory process eventuating in replacement of the colloid vesicles by means of overgrowth of alveolar epithelium, or by invasion and substitution of the alveoli by connective tissue elements (228).

8. Decreased urine elimination (129)

9. Slight albuminuria (129)

10. Increased spinal fluid pressure (168, 214)

11. Anemia (170)

12. Slow pulse (240)

13. Myopia (162)

There are also a number of negative clinical findings that have been reported in comparing dwarf and normal individuals (129):

1. Total nitrogen
2. Urea nitrogen
3. Uric acid nitrogen
4. Ammonia nitrogen
5. Creatinin nitrogen
6. Residual nitrogen
7. Blood sugar units
8. Blood morphology
9. Changes in endocrine glands inconsistent and confusing (168); myxedema and cretinoid stages may occur in animals with typical thyroid hyperplasia (146)

Since it has been determined that dwarf cattle are deficient in thyrotropic hormone (33), it seems worthwhile to consider specific instances of the complex interrelationship of pituitary and thyroid.

In the vertebrates, a delicately balanced relationship is maintained between the amounts of the thyroid hormone produced and stored or released by the thyroid, and of the thyrotropin produced and stored or released by the pars anterior of the pituitary. The thyroid hormone inhibits the production and release of thyrotropin and may even inhibit the making of further thyroid hormone by the thyroid gland itself (1).

In hyperthyroidism, a very low content of thyrotropin is found in blood and urine. In hypothyroid conditions, a greater content of thyrotropin is present in the pituitary and body fluids (1).

A very marked seasonal variation exists in the percentage of iodine present in the healthy, normal-sized thyroid gland of the sheep, beef, and hog. There is in general about three times as much iodine present in the glands in the months between June and November as in the months between December and May (202). The bovine fetal thyroid possesses a strong selective affinity for iodine and contains an appreciable amount of iodine as early as the third month of intra-uterine life (72). It is relatively larger and contains more iodine and phosphorus per unit of body weight than the thyroid from mature animals.

Hyperplasia of the thyroid indicates hyperactivity but not necessarily hyperfunction (146). In the bovine, enlarged thyroid glands (fetal and adult) contain less total iodine and much more total phosphorus than normal thyroids (72). The fetuses possessing enlarged thyroid glands were on the average smaller than fetuses of the same age with normal thyroids.

A study of the thyrotropic hormone content of beef and dairy cattle pituitaries showed that lactating, non-pregnant dairy cattle contained 30 percent more, lactating and pregnant 17 percent more, and dry, non-pregnant 60 percent more hormone than the corresponding classes of beef cattle (233, 1).

In pregnant cows, the thyrotropic content of the pituitaries is greatest in early pregnancy and falls during late pregnancy to approximately the amount present in the non-pregnant animals (1).

Some investigators believe that thyroid insufficiency in the mother is an essential factor in the production of cretinism (150, 191). Insufficient maternal hormone during pregnancy can produce neural defects in the offspring. If sufficient hormone is present in the maternal milk, hypothyroidism in the offspring does not become manifest until after lactation. In the bovine, a thyroid deficiency in the mother due to thyroidectomy was remedied, at least partially, during her pregnancy (213). Apparently, there was a diffusion of the thyroid hormone from the fetus to the maternal circulation. In only partly excised thyroids of rabbits, hormone exhaustion was promoted by pregnancy (10).

A comparison of giant and pygmy rabbits shows that the relative weights of the pituitary, thyroid, thymus, and adrenals are a constant proportion to the total body weight and may be predicted by equation (187).

Data on cases show that the adrenal cortex is adversely affected in primary myxedema so that its functions are depressed. Since this functional

depression has been the basis on which the differentiation between pituitary and thyroid myxedema has been made, it is suggested that reports of pituitary myxedema in the literature may be erroneous.

It is believed that the myxedematous changes incident to the primary hypothyroidism involve the adrenal, either directly or secondarily, through the pituitary gland, or possibly by a combination of both of these factors (52).

It is also postulated that dwarfism in general is the result of insufficiency of the anterior pituitary with fractional deficiencies of hormones concerned with growth and metabolism (216).

In a study of hereditary hypopituitary dwarf mice, the following observations were made (160):

1. Average blood sugar values for fed hereditary hypopituitary dwarfs are slightly, but not significantly, lower than those of fed normal mice.

2. The blood sugar level of fasting dwarfs drops precipitously to a minimum of 68 mg percent after 96 hours. In contrast, normal mice have 103 mg percent after 96 hours of fasting.

3. Sensitiveness of the dwarf is similar to that reported for hypophysectomized animals. This severe hypoglycemia might be attributed to the adrenal-pituitary imbalance in the dwarf.

These dwarf mice can tolerate only 3 percent of the dose of insulin that produces comparable symptoms in normal mice (161).

The adult ruminant is resistant to the hypoglycemic action of insulin. The newborn calf behaves in a similar manner for the first 24 hours, but it then becomes very sensitive to insulin. This sensitivity decreases when the animal becomes about 30 days old (8).

There are a number of factors which modify thyroid and pituitary activity. Those factors which could be involved in the manifestations of the bovine are discussed.

1. Lack of vitamin A leads to increased thyroid activity and increased thyrotropic potency of the pituitary gland (1). The thyroid helps regulate the conversion of carotene to vitamin A (156).

   Cystic pituitary glands have been found in young beef and dairy cattle either suffering from vitamin A deficiency or with a history of early severe vitamin A depletion. No evidence of repair in a cystic pituitary was found in an animal that was vitamin A deficient early in life but later fed adequate amounts of carotene, suggesting that the injury of the gland may be permanent (143).

   Does were deprived of vitamin A 14 weeks before mating. Many of the young rabbits aged from 2 to 8 weeks showed nervous disorders caused by hydrocephalus (157). The hydrocephalic condition was caused by stenosis of the cerebral aqueduct. Paralysis and constriction of the optic nerve were secondary effects.

Thyroid helps regulate conversion of carotene to vitamin A. In view of the importance of vitamin A for the maintenance of pregnancy, the possibility must be considered that a hypothyroid state, combined with a low intake of vitamin A, could result in abortion or dead or weak offspring (156).

2. The morphology of the thyroid gland is affected by environmental temperature. If rats are exposed to temperatures ranging from 12° C to 17° C for more than three days, hypertrophy of the acinar cells of the thyroid occurs (215). If iodine is administered to the rats, it limits hypertrophy but does not prevent it. The hypertrophy is probably caused by a depletion of colloid during the first few days of cold. Besides an environmental effect, there is also a seasonal variation (high in winter, low in summer) which apparently cannot be correlated with environmental temperature (16). It has also been suggested that the degeneration in size and fertility of successive generations of European cattle bred under the hot conditions of the tropics is due to the effects of the high air temperatures causing increased body temperature and inhibition of the development of the anterior pituitary gland in the young animal (96).

3. Goitrogenic foods (cabbage, soy beans, etc.) when fed to animals cause a hyperplastic though hypofunctioning thyroid (1). Plants of the family Brassicaceae appear to be outstanding in this respect, although many foods have not yet been tested (156). Oestrogenic substances have been reported in clover and from the female flowers of the willow (207).

4. The distribution of endemic goiter in England and India is related to the geological distribution of flourine (244). Flourine in drinking water is one factor in the causation of endemic goiter.

5. Adult rats kept under hygienic conditions and fed a high protein diet developed hyperplasia of the thyroid gland (31). Rats kept under unhygienic conditions developed hyperplasia of the thyroid if given a standard diet of bread and milk.

6. Potassium cyanide inhibits the ability of the thyroid gland to take up and store potassium iodide (147).

7. Diets rich in proteins and fats increase the rate of discharge of thyroxine and thyroid activity is more necessary in the oxidation of fats and proteins than of carbohydrates.

8. Manganese apparently has a direct effect on embryonic growth. Injection of manganese directly into albumen of egg increased hatchability and leg length (140). Rats fed cows' milk had a high percentage of deaths of young animals due to congenital debility (48). Analysis showed the diet was deficient in manganese.

9. Comparable cell changes were found in the central nervous system in cretinism, parathyroid tetany, and fatigue (58). All cases had somewhat variable chromatolysis. No marked variations in the nature and course of the affection were found to follow these conditions so strikingly opposite in character. Cellular

alterations representative of steps in the course of the reaction were readily recognized. The severity of the visible symptoms (tetany, cretinism, and exhaustion) was the constant guide in selecting these types.

10. In ringdoves, thyroid size was shown to be influenced by many external and internal conditions, including altitude, diet, season, state of nutrition, unsanitary surroundings, iodine intake, age, intestinal flora, other endocrines, disease, and by sexual and physic states (74).

11. In a study with rabbits, a correlation was found between racial size and total glutathione (88). There was no correlation between size and glutathione between rabbits within a race, but, other conditions being equal, the concentration of glutathione in the young measures the inherent capacity of a race for body size.

12. Muscle development in beef breeds is somewhat more accelerated than in dairy breeds during fetal development, while the rate of linear skeletal development of beef and dairy breeds is about the same (87).

13. Pregnant rabbits were injected with thyrotropic hormone. In every case the gestation was interrupted, either by abortion or the death of the fetuses. The thyroid of the maternal animal was in a state of hyperplasia that was more marked than the normal hyperactivity of pregnancy. The thyrotropic hormone causes interruption of gestation by stimulation of the thyroid gland (239).

14. Desiccated thyroid is effective in the therapy of cretinism (75, 106, 112, 198). In young children it is recommended that therapy start with a daily dose of one-half grain and that the dosage be increased one-half grain at three-week intervals.

15. Thyroidectomized goats administered 1 grm. of thyroprotein daily showed an arrested development of cretinism and stimulated growth approaching normal (185).

Although the identification of dwarfism transmitters has been emphasized in the study of bovine dwarfism, it has not been particularly stressed in the prior research with laboratory animals. In dwarfism in poultry, a few of the "carriers" of dwarfism could be identified by appearance prior to breeding test while others could not be identified without the progeny test (149, 234, 235). In a study of dwarf rabbits, it was noted that a majority of the female transmitters became overfat at maturity and, unless they were bred at frequent intervals, the fat in normal regions accumulated to an abnormal extent. Large deposits of fat were also found in abnormal depots, particularly in the anterior triangle of the neck and about the shoulder girdle (85). In humans, the individuals with a predisposition for hypothyroidism were described as rather squat, dumpy, thick-necked and potbellied. Obesity is common (155). It has also been noted that families of dwarfs are generally short of stature (196).

Selection for small size in mice has shown that the frequency of a dwarf gene was greatly increased in this strain. This was not true in lines selected for medium or large size. It appeared that the heterozygous individuals were enough smaller on the average than homozygous normals to have approximately twice the chance of being selected for breeding purposes and producing offspring (134, 236). A similar situation has been postulated to account for the increased frequency of the dwarf gene in beef cattle (93).

The head contour has been studied as a means of identifying mature horned Hereford cattle heterozygous for the dwarf gene (93). Normal growth tendencies in the basal bones of the skull are in the direction of increased length relative to width as age advances. Brachycephaly is characteristic for young animals and as age advances the skull becomes more and more dolicephalic. The picture presented by the nasal bones of cretin skulls is in the direction of retarded growth. This is probably the primary factor, but that is not the only one since cretin skulls are often broader than normal skulls of the same size (59).

There is also a forward shift of the nasion and posterior parts of the cranium. Restricted growth in cartilage bones, together with a similar disturbed growth in the ethnoid bones which form a rather inflexible base, cramp cranial and brain growth in the anterior-posterior direction. In these, the normal potentialities seem to be almost undisturbed as is indicated by the general development of the cranial vault. This cramping results in both lateral and posterior expansion of the cranium, the direction of least resistance, to accommodate the relatively more developing brain.

Other characteristics commonly associated with brachycephaly are shortened inferior and superior maxillary bones, and change in shape and saddling of the nose.

The skull is affected in heterozygous Herefords as shown by the median profile and head measurements (93). Based on the observations of thyroidectomized animals and the characteristics of adult myxedema, there do appear to be other factors which should be considered in the identification of dwarfism transmitters in beef cattle.

1. Shortened and thickened long bones
2. Asymmetrical skull
3. Prognathic lower jaw
4. Below normal size
5. Impaired hearing
6. Dry, coarse, and brittle hair
7. Epiphyseal dysplasia, lesions due to failure of bone formation in cartilage
8. Normocytic, normo- or hypochromic anemia
9. Constipation
10. Above normal serum cholesterol
11. Above normal serum carotene
12. Above normal serum protein
13. Above normal cerebrospinal fluid pressure
14. Hypersensitive to cold
15. Insulin sensitivity
16. Impaired vision, including cataracts of the lens and structural variations of the iris
17. Fat deposition in the anterior triangle of the neck

18. Delayed tooth eruption and development
19. Brachycephilia
20. Papilledema
21. Below normal BMR
22. Decreased fertility, including abortion and stillbirths

Progeny tests with beef cattle usually require a combination of several mating systems. A method for combining the results of different mating systems encountered in animal breeding has been reported (14).

I. Mating to recessive type:

$$Paa = \frac{1}{1 + (\frac{1}{2})} \quad n$$

Paa = probability of homozygosity.
n = number of offspring. Offspring may be from a single female or a number of females.

II. Mating to heterozygous females:

$$Paa = \frac{1}{1 + (3/4)} \quad n$$

Offspring may be from a single female or a number of females.

III. Matings to daughters of heterozygotes:

$$Paa = \frac{1}{1 + (7/8)} \quad n$$

Only a single offspring from a single female.

IV. Mating to full sisters:

$$Paa = \frac{1}{1 + 2\ (5/6)} \quad n$$

A single offspring from each full sister.

V. Matings to paternal half sisters: Same formula as for matings to daughter of heterozygotes.

VI. Mating to daughters: Same formula as for matings to daughters of heterozygote. If the male is tested by different mating methods, the results can be combined by combining the n-values.

The conversion factor of n for calculating all observations on the basis of P = 7/8 is given:

	Values of P			
	1/2	3/4	5/6	7/8
Conversion factor of n	5.19	2.15	1.37	1.00

GLOSSARY

ABDUCT. To move away from the axis of the body or of one of its parts.

ABLATION. The removal of a part of the body, as by amputation, or of any growth or noxious substance.

ACHONDROPLASIA. A disturbance in the normal process of ossification in cartilage, dating from intra-uterine life, resulting in arrested growth of the long bones and a condition of stocky dwarfism; the head is large and abdomen prominent. The extremeties are disproportionately short in comparison with the torso.

ACINOUS. Resembling a bunch of grapes; noting certain glands the excretory ducts of which start from little sacs arranged in clusters like grapes.

ACROCEPHALY. Having a high or peaked head.

ADENOMATOSIS. A condition marked by the formation of multiple glandular overgrowths.

AGENESIS. Absences or imperfect development of any part.

AMAUROSIS. A total loss of vision without discoverable lesion in the eye structures or optic nerve.

AMENTIA. A form of confusional insanity marked especially by apathy, disorientation, and more or less stupor.

ANKYLOSIS. Stiffening or fixation of a joint.

ANTITHENAR. Hypothenar. The fleshy mass at the inner (little finger) side of the palm.

ANTRUM. (1) Any nearly closed cavity, particularly one with bony walls. (2) The pyloric end of the stomach partially shut off, during digestion, from the cardiac end by the prepyloric sphincter.

APLASIA. Congenital absence of an organ or any part.

ARHINENCEPHLIA. An absence or rudimentary state of the rhinencephalon, or olfactory lobe, on one or both sides, with a corresponding lack of development of the external olfactory organ.

ATAXIA. A loss of the power of muscular coordination.

ATELIOSIS. Incomplete development of the mind or the body or any of its parts; infantilism.

ATHYREA. Absence of the thyroid gland, or deficiency of the thyroid secretion.

ATRESIA. Congenital absence or pathological closure of a normal opening or passage.

BIFID. Split or cleft; separated into two parts.

BOMBOSE. Convex rounded surface.

BRACHYCEPHALY. Having a disproportionately short head.

BRADYCARDIA. Abnormal slowness of the heart beat.

CACHEXIA. A general lack of nutrition and wasting occurring in the course of a chronic disease.

CANTHUS. Either extremity of the rima palpebrarum or slit between the eyelids.

CEBROCEPHALUS. A monster with features like those of a monkey, slightly marked or absent nose and close-set eyes.

CELIAC disease. Intestinal infantilism. A condition seen chiefly in young children, marked by the passage of large, whitish, frothy, and offensive stools, containing quantities of unsplit fat.

CEREBROSPINAL. Relating to the brain and the spinal cord.

CHOLESTEROLEMIA. Presence of cholestrin in the blood.

CHONDRODYSPLASIA. (see ACHONDROPLASIA).

CHONDRODYSTROPHIA. (see ACHONDROPLASIA).

CHONDRODYSTROPHY. (see ACHONDROPLASIA).

CHOREA. A disorder, usually of childhood, characterized by irregular, spasmodic, involuntary movements of the limbs or facial muscles.

CRETIN. An idiotic dwarf, the subject of congenital myxedema, occurring both sporadically and endemically.

CRIBRIFORM. Sieve-like; containing many perforations.

CYANOSIS. A dark bluish or purplish coloration of the skin and mucous membrane due to deficient oxygenation of the blood.

CYST. An abnormal sac containing gas, fluid, or a semi-solid material.

DEBILITY. Weakness.

DIASTEMA. (1) An interval between two teeth. (2) The angle formed by the lingual surface of the upper canine or cuspid tooth and the proximal or anterior surface of the premolar.

DIPLEGIA. Paralysis of corresponding parts on both sides of the body.

DOLICHOCEPHALIC. Having a disproportionately long head.

DROPSY. Hydrops; an excessive accumulation of clear, watery fluid in any of the tissues or cavities of the body.

DYSGENESIS. Sterility.

DYSPLASIA. Abnormal tissue development.

DYSTOCIA. Difficult parturition.

ECTOMY. Operative removal of any organ or gland.

ENDEMIC. (1) Present in a community, noting specifically a disease which prevails more or less continuously in a given region. (2) The constant prevalence of a disease in a community, as distinguished from an epidemic.

ENDOCHONDRAL. Within a cartilage or cartilaginous tissue.

EPICANTHUS. A fold of skin extending from the root of the nose to the inner termination of the eyebrow, overlapping the inner canthus.

EPIPHYSIS. A part of the long bone developed from a center of ossification distinct from the shaft and separated at first from the latter by a layer of cartilage.

ETIOLOGY. The causes of disease.

EXOPHTHALMIA. A prominence of the eyeball.

EXTIRPATION. The entire removal of an organ or part or of a pathological structure.

FURFURACEOUS. Branny, scaly, scurfy.

GARGOYLISM. Chondrodystrophy, congenital corneal opacities, hepatosplenomegaly, and mental deficiency.

GRAVES' DISEASE. Exophthalmic goiter.

HEPATOSPLENOMEGALY. Enlargement of the liver and spleen.

HERMAPHRODITE. An individual whose genital organs have the characters of both male and female in greater or less degree.

HYDROCEPHALUS. A condition, usually congenital, marked by an extensive effusion of serum into the cerebral ventricles, dilating these cavities, thinning the brain, and causing a separation of the cranial bones; there may also be an accumulation of fluid in the subarachoid space.

HYPER-. A prefix denoting excessive, above the normal.

HYPERMETROPIA. Hyperopia. Long-sightedness.

HYPERTELORISM. Extreme width between the eyes.

HYPERTROPHY. Overgrowth; general increase in bulk of a part or organ, not due to tumor formation.

HYPO-. A prefix, equivalent to "sub". Denotes (1) location beneath something else; (2) a diminution or deficiency.

HYPOPHYSIS. Pituitary body, a small, two-lobed body at the base of the brain.

HYPOPLASIA. (1) Defective formation, incomplete development of a part. (2) Atrophy due to destruction of some of the elements and not merely to their general reduction in size.

KYPHOSIS. Cyphosis, a curvature of the spine, hump-back; an abnormal curvature of the spine with convexity backward, due to caries and destruction of the bodies of the affected vertebrae.

LORDOSIS. Anteroposterior curvature of the spine, generally lumbar with the convexity looking anteriorly.

MACROGLOSSIA. Enlargement of the tongue.

MICROCEPHALIC. Abnormal smallness of the head.

MONGOLISM. Idiocy marked by a cheerfulness of disposition, vivaciousness, and imitativeness. A flattened skull.

MORQUIO'S DISEASE. Osteochondrosis, familial osseous symmetrical dystrophy.

MYOPIA. Short-sightedness.

MYXEDEMA. A trophic disorder marked by a hard edema of the subcutaneous tissues, dryness and loss of hair, subnormal temperature.

MYXOMA. A tumor composed chiefly of polyhedral or stellate cells embedded in a soft matrix containing mucin.

NANUS. A dwarf, a pygmy.

NEONATAL. Relating to the period immediately succeeding birth.

NIDATION. The formation of the decidua capsularis.

NYCTALOPIA. Night blindness, inability to see as well as normal at night or in dim light.

NYSTAGMUS. Rhythmical oscillation of the eyeballs, either horizontal, rotary, or vertical.

OLIGODENDROGLIA. Mesoglia, neuroglia tissue containing cells of size intermediate between the mossy and the spider cells.

OXYCEPHALIA. The occurrence of a high, vertical index in a skull.

PALPEBRA. Eyelids.

PAPILLEDEMA. Choked disc, inflammation of the optic nerve at its entrance into the retina.

PARA-. A prefix denoting (1) a departure from normal, (2) an involvement of two like parts, as the two lower extremities.

PARESIS. Partial or incomplete paralysis.

PISIFORM. Pea-shaped or pea-sized.

PITUITARY. (see HYPOPHYSIS).

POLYHYDRAMNIOS. Dropsy of the amnion, an excess in the amount of amniotic fluid.

PROGERIA. A condition characterized by a mixture of infantilism and premature senility; the subject presenting the mental and physical characteristics of old age, with persistence of the milk teeth, absence of the hairy growth normal at puberty, and persistence of the thymus.

PROGNATHISM. Abnormal projection forward of one or both jaws.

PUNCTATE. Marked with points or dots differentiated from the surrounding surface by color, elevation, or texture.

SCAPHOCEPHALIC. A long, narrow skull with a more or less prominent ridge along the prematurely ossified saggital suture.

SCOLIOSIS. Lateral curvature of the spine.

SPASM. An involuntary, convulsive, muscular contraction; convulsion; cramp.

SPLENOMEGALIA. Enlargement of the spleen.

SQUAMA. A thin plate of bone.

STENOSIS. A narrowing of any canal, a stricture.

SYNCOPE. Fainting, a swoon; a sudden fall of blood pressure or failure of the cardiac systole, resulting in more or less complete loss of consciousness.

TACHYCARDIA. Very rapid action of the heart.

THYROID. A ductless gland lying in front of the upper part of the trachea; it furnishes an internal secretion of influence upon metabolism.

THYROTROPIC HORMONE. A hormone produced by the anterior lobe of the pituitary gland which influences the development and activity of the thyroid.

THYROTOXICOSIS. Poisoning by an excess of thyroid secretion.

TROPHIC. Relating to or dependent upon nutrition.

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